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January 1977

NEWS & FEATURES From NIH

Research Advances

NICHD GRANTEES ARE USING CALCIUM THERAPY FOR SOME PREMATURE BABIES

National Institute of Child Health and Human Development grantee scientists are administering oral calcium supplementation therapy to premature or oxygen-deprived newborn infants.

Hypocalcemia, or low serum calcium affects 30 percent to 50 percent of these high risk infants. Although the importance of calcium metabolism is well known for cellular function and skeletal development, there is little information concerning the possible modes of therapy for the prevention of hypocalcemia.

Maintenance of calcium balance during the transition from fetal to neonatal life requires some major physiologic alterations on the part of the newborn. The infant is suddenly removed from an environment where he was receiving a daily transplacental influx of 130 to 150 mg of calcium per kilogram (2.2 lbs.) of body weight to an environment where he must depend on breast or bottle-feeding during a period when oral intake is usually minimal.

In this study 16 infants born at the Cincinnati General Hospital between August 1973 and December 1974 were selected. Eight calcium-supplemented infants were individually matched with eight control infants for gestational age and one-minute Apgar test scores. The Apgar test score is a measure of an infant's survivability predicted by such factors as pallor and cry, and expressed on a scale of one to 10.

Between the ages of 12 hours and three days one neonate in each matched pair received on a 24-hour basis the oral supplement of 75 mg of elemental calcium per kilogram of body weight. The calcium was administered as a syrup (Neo-Calglucon) given immediately before or within one hour after feeding.

(more)

CALCIUM (CONT'D)

Blood samples were obtained from the mother within six hours of delivery, from the umbilical cord, and from the infant at 12, 24, 36, 60, 84, and 108 hours after delivery. Analysis of the samples showed that mean serum calcium values for the mother, the cord bloods, and the infants prior to 12 hours of age were the same for the two groups.

However, after the supplementation began the treated infants serum calcium rose to 9.5 mg per deciliter (0.21 pints) as opposed to the control infants 8.1 mg per deciliter.

While receiving the calcium supplement, and for more than a day afterward, none of the treated infants were hypocalcemic. Three of the eight controls experienced hypocalcemia on at least one occasion. Hypocalcemia was defined as serum calcium below 7.0 mg per deciliter in premature and 8.0 mg per deciliter in full-term infants. During the first 36 hours after supplementation was discontinued serum calcium in the treated group remained significantly higher (9.7 mg per deciliter) than in the controls (7.1 mg per deciliter).

The blood samples were also analyzed for serum total magnesium, phosphate, 25-hydroxy-vitamin D, and parathyroid hormone. All these factors are important in maintaining calcium balance, and calcium supplementation had no apparent effect upon serum levels.

The main side effects of calcium supplementation were an increased frequency of bowel movements, and the occurrence of transient borderline hypercalcemia (above normal serum calcium) in one of the supplemented infants. The more frequent bowel movements did not affect weight gain, but the one example of mild hypercalcemia emphasizes the need for monitoring serum levels when added calcium is given.

(more)

CALCIUM (CONT'D)

The bone changes of nutritional rickets in very small premature infants have been thought to be related to vitamin D deficiency. The results of this study possibly indicate that they are instead related to a prolonged lack of calcium. For both premature and highly stressed newborns, oral calcium supplementation, these findings suggest, may be useful in preventing early neonatal hypocalcemia and aid in subsequent bone mineralization.

This research was published in the December 1976 issue of *The Journal of Pediatrics* by David R. Brown, M.D., Reginald C. Tsang, M.B.B.S., and I-Wen Chen, Ph.D., of the University of Cincinnati College of Medicine.

Research Advances

NEW SYNTHETIC HORMONE IS USED TO TREAT ANGIOEDEMA

NIH scientists have shown that a new synthetic hormone, Danazol, prevents potentially life-threatening attacks of hereditary angioedema (HAE). In addition, the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Child Health and Human Development (NICHD) investigators have found that the drug acts to correct the inherited biochemical abnormality believed to cause the disease.

Hereditary angioedema is a rare but serious condition characterized by episodes of swelling of the hands, feet, face, or airway passages and recurrent abdominal pain. Although these attacks can occur without provocation, anxiety, stress, or minor trauma, such as dental work, have been associated with an increased incidence of attacks. Deaths due to HAE, usually caused by airway obstruction, have been reported to be as high as 30 percent.

Lacking effective means of stopping an attack once it starts, patients with HAE have relied on long-term use of various drugs to prevent the attacks. However, these agents can produce serious side effects, thus limiting their usefulness. In addition, the prolonged use of one class of these drugs -- androgens -- by women with HAE can result in masculinization.

The NIH researchers, therefore, decided to study the effectiveness of a new androgen, Danazol, which has a reduced potential for producing masculinization. Five young women and four men who had a history of one or more HAE attacks each month received randomized courses of either Danazol or a placebo. Each course lasted 28 days, unless an attack occurred. A new course was begun either after successful completion of a 28 day course, or after an

(more)

attack subsided. Neither the physicians nor the patients knew when a patient was taking Danazol or a placebo.

During 46 Danazol courses completed by the nine patients, only one HAE attack occurred. Side effects of the drug were minimal: some weight gain in all patients, and menstrual irregularity in the women. However, the hormone did not produce virilization of the women nor affect the sexual potency of the men.

In sharp contrast, during the 47 courses of placebo in the same patients, 44 HAE attacks occurred.

In addition, the Bethesda researchers found that Danazol reversed the biochemical defect thought to be the cause of HAE - low amount and diminished activity of a protein which inhibits the first component of complement (a series of interacting serum proteins involved in immune responses). While on Danazol, the amount and activity of this inhibitor protein in these patients climbed to almost normal levels. One patient, who discontinued Danazol after 60 days experienced a decrease in the level of this protein until she resumed taking Danazol.

The scientists hope that any possible side effects of long term use of Danazol might be offset by lower dosages. Most of the patients, all of whom have chosen to remain on Danazol, have been able to decrease their daily dosages. No further toxicity has been seen even in those patients who have been on Danazol for six months.

Further study of Danazol's action in hereditary angioedema may provide a greater understanding of the underlying factors controlling and modifying this, and possibly other, genetic diseases.

(more)

ANGIOEDEMA (CONT'D)

The team of investigators, Drs. Jeffrey Gelfand, David Alling, and Michael Frank of NIAID and Dr. Richard Sherins of NICHD, reported their study in the December 23, 1976 issue of *The New England Journal of Medicine.*

#

Research Advances

CONSENSUS IS REACHED ON HIGH BLOOD PRESSURE DIAGNOSIS AND TREATMENT

A recent report of the National High Blood Pressure Education Program marks "the first time this country's medical associations and authorities have reached a consensus on an approach to diagnosis and treatment of high blood pressure," according to Dr. Robert I. Levy, Director of the National Heart, Lung, and Blood Institute.

The *Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure* underlies agreement over when and/or what treatment is appropriate for high blood pressure. Dr. Levy noted that it provides a cost-effective, practical basis for addressing a health problem that is estimated to affect 23 million or more Americans.

The report emphasizes that early detection of high blood pressure is only part of the problem and that getting a person to begin and maintain proper treatment represents perhaps an even greater challenge. Groups or individuals who plan to measure blood pressure must ensure an adequate system for follow-up blood pressure measurements to confirm suspected elevation and provide prompt referral of people with consistent elevated blood pressure. Screening efforts should continue, says the report, but if all physicians regardless of specialty, as well as dentists and other medical specialists, would measure blood pressures routinely, the need for mass screening efforts would greatly decrease.

The report recommends that:

* Virtually anyone with a diastolic pressure of 105 mmHg or more should be treated with antihypertensive drugs.

* Drug treatment may or may not be appropriate for persons with diastolic

(more)

pressures between 90-104 mmHg.

* Only a few, limited tests are needed to evaluate properly most people with high blood pressure and that hospitalization is rarely needed.

* A simple, "stepped-care" appproach to drug treatment should be used.

The report describes dosages, side effects and contraindications for antihypertensive medications including propranolol, a drug recently approved for the treatment of hypertension by the Food and Drug Administration.

The report was endorsed by the High Blood Pressure Coordinating Committee composed of major medical organizations who act in a mutually advisory and coordinating capacity to the National High Blood Pressure Education Program (NHBPEP). A listing of the organizations represented on the Coordinating Committee as well as members of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure is available.

The report was published in the January 17, 1977, issue of the *Journal of the American Medical Association*. Copies are available from the High Blood Pressure Information, 120/80 National Institutes of Health, Bethesda, Maryland 20014.

#

Photo Feature

PROGRESS REPORTED TOWARD SCHISTOSOMIASIS VACCINE

Progress in immunization against schistosomiasis, an unconquered parasitic disease, has been reported by Dr. George V. Hillyer, head of a research group at the University of Puerto Rico.

Appearing in the December 1976 issue of *Federation Proceedings*, monthly publication of the Federation of American Societies for Experimental Biology, the report, "Can we Vaccinate Against Schistosomes?", is one of eight scientific papers written by researchers of the Minority Biomedical Support Program which is funded by NIH's Division of Research Resources.

Schistosomiasis is a disease of man and animals caused by blood flukes (parasitic worms) of the genus *Schistosoma*. The parasites causing human disease are found in the Orient (an estimated 200 million Chinese are infected), portions of Africa including The Nile, South America (especially Brazil), and some of the islands of the Caribbean. It is estimated that 300,000 persons are infected in Puerto Rico. Infection does not occur in the United States, but is present in the bloodstream of some immigrants entering the country.

It takes three to make a schistosomiasis infection--mammalian host, intermediary snail host, and the parasitic schistosome (a blood worm or fluke).

Transmitted by excretion, a schistosome egg passes through the intestine of an infected mammalian into fresh water and hatches into a larval stage called a miracidium. The miracidium infects a specific type of snail, and after several developmental changes in the snail, the parasite evolves into a fork-tailed larva known as cercaria. When the cercaria leaves the mollusk, it propels its way through the water in search of a mammalian host.

(more)

SCHISTOSOMIASIS (CONT'D)

When it makes contact with a human being, it penetrates the skin and enters the body. The cercaria eventually turns into mature schistosomes which live in the bloodstream. The parasite, in its adolescent stage, matures and mates, and the female lays its eggs. The adult worms remain in the blood vessels surrounding the intestinal tract or urinary bladder, their eggs traveling through the bloodstream to various organs of the body, particularly the liver.

The victim generally experiences itching, pain, weakness, and a shortened life span.

It has been determined that when animals and man are infected with schistosomes, they acquire resistance to re-infection, and the resistance is immunologic in origin. Apparently the cells produce a toxicity which is induced by an antigen.

Dr. Hillyer's group has been conducting long-range studies on immunology induction in mice and hamsters before infection. In recent laboratory experiments, the researchers have found a complex of polyadenilic-polyuridylic acid (poly AU) to be a powerful stimulant of antibody production when inoculated into animals together with an antigen.

By use of *Fasciola* antigens (from another kind of fluke) combined with one injection of poly AU, the researchers achieved a 67 percent reduction in worm burden (schistosome infection) in mice. When two inoculations of poly AU were used, the worm burden reduction was 74 percent, according to Dr. Hillyer.

They also report that mice immunized with *Fasciola* antigens had four-fold

(more)

or higher titers of antibodies to schistosomes than mice infected with schistosomes but not immunized.

Concluding that *Fasciola* antigens prime the host to have a secondary reaction when infected with schistosomes, the current work of the Minority Biomedical Support group at the University of Puerto Rico is now directed toward purifying the antigens involved in this protection.

The researchers are optimistic that eventually a vaccine can be prepared which will give total protection against this parasitic disease now so prevalent in China, Africa, South America, and Puerto Rico.

Fork-tailed larva (400 microns long) can penetrate the skin and eventually turn into mature schistosomes. Researchers at the University of Puerto Rico, supported by NIH's Division of Research Resources, are making progress in the effort to develop a vaccine against schistosomiasis--a parasitic disease affecting over 300,000 persons on the island. (NIH Photo #1574)

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January 1977

NEWS & FEATURES From NIH

News Feature

CYCLOPHOSPHAMIDE PRETREATMENT HELPS MICE SURVIVE MALARIA

Pretreatment with the drug cyclophosphamide (Cy) enables mice to survive subsequent infection with a lethal strain of malaria, according to a recent report by Dr. John Finerty of the National Institute of Allergy and Infectious Diseases (NIAID) Laboratory of Microbial Immunity and Dr. Edward Krehl of Trudeau Institute, Saranac Lake, N.Y. This protection appears to result from the drug's enhancement of the activity of T cells, the thymus-dependent lymphocytes that mediate cellular immune responses.

The effect of cyclophosphamide on the immune system apparently varies with its time of administration. If given simultaneously with infectious organisms or after an infection is established, Cy is a potent suppressor of the immune response. However, several studies have shown that Cy can increase the immune response to certain nonviable antigens if administered prior to immunization with them.

To determine the effects of Cy on the immune response to malaria parasites, the researchers administered the drug to mice 48 hours before infecting them with a lethal strain of malaria, *Plasmodium berghei yoelli* 17XL. At various times during an infection, the presence of delayed hypersensitivity, an indication of T cell activity, was determined by injecting the animal's footpad with a challenge dose of malaria antigen and then measuring any increase in the thickness of the footpad.

Mice pretreated with Cy exhibited a delayed hypersensitivity (DH) response which peaked at day two of infection but decreased sharply on day four. These animals, however, overcame the lethal infection unlike a group of similarly infected mice which had not received Cy. The DH response of the untreated

(more)

animals did not peak until day six, shortly before their deaths.

Drs. Finerty and Krehl next examined the relationship between the DH response and the level of parasites in the blood of Cy treated and untreated mice infected with the same lethal organisms. They found parasites in the blood of the Cy mice from day two, although the numbers did not increase until day four, peaked at day 11, and disappeared by day 24. Thus, the low level of parasitemia coincided with the high DH response seen in Cy mice; likewise, the subsequent increase in parasitemia coincided with the decrease in DH. In contrast, the level of parasitemia in a non-Cy group of mice rose sharply from day two until their deaths on day nine, paralleling the weak DH response observed in other non-Cy mice.

These results suggest that T cells may play a vital role early in malaria infection. The scientists feel, therefore, that pretreatment with cyclophosphamide enhanced the T cell reactivity and was responsible, in part, for protecting the mice against the lethal infection.

They point out, however, that the mechanisms whereby Cy alters the immune response, either by suppression or enhancement, are still not understood. Thus, it is possible that pretreatment with cyclophosphamide could have suppressed the response of B cells, antibody-producing lymphocytes. Such antibody may interfere with the development of immunity to parasites. Studies are now underway to investigate the mechanisms involved.

These findings, reported in the October, 1976 issue of *Infection and Immunity*, also indicate that host immunity can be manipulated by chemical agents in a situation in which protective means of immunization do not exist.

#

January 1977

NEWS & FEATURES From NIH

News Feature

VIRAL MICROFILAMENTS FOUND IN PAGET'S DISEASE PATIENTS

Investigators at the University of Southern California, Los Angeles, studying bone cells in patients with Paget's disease, a painful bone deformity, have observed particles in the cell nuclei which resemble viral microfilaments. Similar particles have been found in nerve cells of patients with subacute sclerosing panencephalitis (SSPE), a disease which has been linked to a measles-like virus.

Barbara G. Mills, M.D., and Frederick R. Singer, M.D., note that Paget's disease, found in about three percent of the population over age 40, often progresses slowly, in a somewhat unpredictable way before the pain develops. It is frequently diagnosed in an early stage from radiographs made as a result of other complaints. The cause has been entirely unknown, and the treatment therefore is symptomatic.

The investigators report that about a fourth of the nuclei in osteoclasts from all 18 of their patients with Paget's disease contained microfibrils, but other cells from the same subjects did not. Osteoclasts, which have several nuclei, are known to remove bone in the normal process of remodeling.

This research, supported by NIH's National Institute of Dental Research, confirms a recent European discovery of nuclear inclusions in Paget's disease. However, it discounts the possibility that the microfilaments could be derived from a papovavirus because the patients have low levels of antibody to that virus. The California investigators rule out this and several other sources of nuclear inclusions, and then call attention to strong similarities between the microfilaments they saw and those seen in patients with SSPE. Both diseases cause localized damage to tissues and have long periods of

(more)

PAGET'S DISEASE (CONT'D)

latency.

Because the filaments are not the same as a mature virus or virion, the scientists cannot be sure of the origin or true significance of the inclusions until recognizable virions or a viral antigen are identified. Perhaps further study following their clues may clarify the cause of this painful bone disease.

The microfilaments were always observed inside the nucleus of an osteoclast unless nuclear degeneration had begun. Then they might be found in nearby cytoplasm. In both SSPE and Paget's disease, filaments were either dispersed at random or packed in a hexagonal crystalline pattern. The only noticeable difference between SSPE and Paget nuclear inclusions that the investigators were able to discover was that the filaments appeared to be somewhat stiffer in bone than in nerve cells.

The pathologists could not find nuclear inclusions in any cell type in 60 other patients with a variety of different calcium and bone disorders, or in normal alveolar bone from the jaws of five dental patients.

Radiographs of pagetic bones in the early stages of the disease show that the bones thin in a characteristic pattern of "punched out" circles. When long bones are affected, they often bow under the patient's weight. Later, the body seems to try to compensate by depositing so much extra calcium that unsightly thickening occurs. Some bones are damaged while others appear to be normal. Nagging bone pain and muscle cramps are common in advanced Paget's disease.

These findings were published in *Science*.

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Photo Feature

NEW UNIVERSITY CENTER TREATS BONE DISEASES

The bone disease center at the Washington University Medical Center in St. Louis is now regarded as one of the world's most comprehensive facilities to treat diseases affecting bone tissues.

Using a 25-bed General Clinical Research Center, which is funded by NIH's Division of Research Resources, experts in endocrinology, pathology, internal medicine, radiology, nuclear medicine, medical genetics, pediatrics, and orthopedic surgery pool their knowledge in both clinical and research areas.

Dr. Louis V. Avioli, a specialist in the study and treatment of bone diseases, joined the Washington University School of Medicine in 1966 and is now director of the Division of Bone and Mineral Metabolism. His continued dedication and activity in the area of bone disease has provided the mainspring for the creation of the internationally-known "Bone Center."

More than 1,500 persons with bone disease have come to the center since 1966. Often their disease is rare, or thought to be incurable, or may require detailed study before any diagnosis or treatment can be determined.

Evidence of dramatic progress in the diagnosis and treatment of bone disease by Dr. Avioli and his associates is demonstrated by "miracle cure" stories related by present and former patients of the center. Among them are:

* A 14-year old boy from Australia, confined to a wheelchair for four years, with a severe form of vitamin D resistant rickets, walks out the door with the help of crutches with hope of discarding them forever.

* A Seldon, New York youth, unable to walk or stand due to a resident form of rickets, now plays football with his friends.

(more)

CENTER (CONT'D)

* A middle-aged Hawaiian, suffering from severe osteoporosis of the spine, in constant pain and experiencing actual physical shrinkage, now reports that he is "overjoyed by return of muscle strength in my forearms; my back feels stronger, and I no longer fear that my legs won't hold up."

* A choreographer, suffering from progressive loss of bone, became immobilized and hunched over in a wheelchair most of the time--but now, after diagnosis and treatment, is able to walk about with a cane.

The cases of people walking on their own after being confined to a wheelchair are common at the Bone Center. Over the years, it has become an international referral for bone disorders. The areas of bone study and treatment include Paget's disease, various types of rickets disorders, chronic renal disease, osteogenesis imperfecta, effects of cortisone on bone metabolism, the relationship of vitamin D and bone loss, and bone reduction in diabetics and chronic alcoholics.

A detailed article by Phyllis Hillinger about the Washington University School of Medicine Bone Center was just recently published in their quarterly publication, *Outlook*. This seven-page description of the Bone Center has been reprinted (with permission) by NIH's Division of Research Resources, and is identified as "Bone Disease Study at the General Clinical Research Center." A free single copy is available by writing to the Office of Science & Health Reports, Division of Research Resources, National Institutes of Health, Bethesda, Maryland 20014.

(more)

CENTER (CONT'D)

Bone losses in alcoholic and diabetic patients are major study areas at the Bone Center, headed by Dr. Louis V. Avioli, of the Washington University School of Medicine, St. Louis, Mo. NIH's Division of Research Resources supports the 25-bed General Clinical Research Center where bone disease patients from all over the world are examined and treated. (NIH Photo #1575)

(more)

CENTER (CONT'D)

Absorption of calcium from the patient's food is of prime consideration in the overall dietary treatment of various bone diseases. The Tri-Carb Scintillation Spectrometer being used above is located in the General Clinical Research Center, which is supported by NIH's Division of Research Resources. This unit measures the calcium absorbed by the skeleton. Clinical researchers at the Washington University Medical Center are delving into the relationship between vitamin D and bone loss. (NIH Photo #1576)

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News Feature

RECOMMENDATIONS RELEASED FOR RESEARCH INVOLVING PRISONERS

HEW Secretary David Mathews has released the Report and Recommendations on Research Involving Prisoners compiled by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

The Commission was established in late 1974 under the National Research Act, Public Law 93-348, and was required to make recommendations with regard to research on human subjects generally, and on prisoners, the mentally infirm, psychosurgery, and the fetus. Recommendations on fetal research appeared in August 1975 and were promptly implemented by DHEW.

The Commission has carried out an extensive study of the nature of research on prisoners conducted in the United States. In addition, Commission members made visits to four prisons, including interviews with inmates who had been research subjects. Consultants to the Commission conducted similar studies at five additional prisons. Public hearings were held to hear testimony from prisoner advocates, prisoner legal services, research scientists, and members of the general public.

The Commission also sponsored a National Minority Conference on Human Experimentation to insure that the voices of the various minority groups would be heard. Finally, in a series of deliberative meetings open to both press and public, the Commission considered its own observations and those of experts who studied foreign methods of non-prison drug testing, alternatives to the use of prisoners, and sociological perspectives in the use of prisoners.

In summary, the Commission's five recommendations are:

* Studies of the causes and effects of imprisonment and of prison life

(more)

may be conducted provided that the risks are minimal and do not seriously inconvenience the subject.

* Research may be conducted on new or accepted methods of diagnosis or treatment which are intended to improve the health or well-being of the individual prisoners and have a reasonable chance of success.

* Other types of research may not be conducted unless the research is found by the head of a responsible Federal department, in consultation with a national ethical review body, to fulfill an important social and scientific need. The reasons for involving prisoners must be compelling, and the conditions of imprisonment such as to insure a high degree of voluntariness on the part of the subject and openness on the part of the correctional institution.

* The investigators must in all instances be competent, the research facilities adequate, and the research subject to review by an institutional review board including among its members prisoners or prisoner advocates as well as meeting all other requirements for institutional review boards.

* Current research projects, subject to regulation by the Secretary of HEW, that cannot meet these requirements should be permitted to continue not longer than one year from the date of publication of the recommendations, or until completed, whichever is earlier.

Under the terms of the National Research Act, the Secretary must seek public comment on these regulations before either rejecting or implementing them. Either action must be completed within a period of 180 days.

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NEWS & FEATURES From NIH

January 1977

News Feature

ENVIRONMENTAL FACTORS ARE RELATED TO CANCER RISKS

A new geographical study of cancer death rates among the nonwhite populat in the United States further supports a relationship between environmental factors and cancer risks, the National Cancer Institute (NCI) has reported.

The Atlas of Cancer Mortality Among U.S. Nonwhites: 1950-1969 describes cancer death rate patterns which often were similar for nonwhites and whites, Institute scientists indicated. Further study will be necessary before many of the specific reasons for these patterns can be identified, they said.

The *Atlas* is a companion publication to the *Atlas of Cancer Mortality for U.S. Counties: 1950-1969*, which describes geographic patterns for cancer among whites. Authors of both volumes are Dr. Thomas J. Mason, Frank W. McKay, and Drs. Robert Hoover, William J. Blot and Joseph F. Fraumeni, Jr., of the NCI Environmental Epidemiology Branch.

Both publications are based on tabulations of deaths for 35 types of cancer compiled by the National Center for Health Statistics in the U.S. from 1950 through 1969 by county of usual residence, type of cancer, sex, and race (white and nonwhite). Annual rates based on these deaths were published by NCI in 1974. The major U.S. nonwhite groups are blacks, American Indians, Chinese and Japanese.

As with their previous publication, the NCI scientists believe the new *Atlas* should be used to identify communities or regions of the U.S. where investigations into possible environmental factors may prove most fruitful.

The similarity in geographic patterns of cancer for whites and nonwhites was particularly striking for cancers of the breast, colon, rectum and esophagus,

(more)

which showed generally high rates in the North and low rates in the South. Cancers of the larynx, bladder and ovary also had above-average rates in the North.

For lung cancer, both white and nonwhite males experienced high rates in northern urban areas and generally low rates in the South. The unusually high rates for white males along the Gulf and Southeast Atlantic coasts were much less pronounced among nonwhites.

Cancers of the uterine cervix had above-average rates primarily in rural areas of the South. The especially high rates for cancers of the uterine cervix among nonwhites reflect the higher cervical cancer risks of black women, the scientists indicated.

The Atlas of Cancer Mortality Among U.S. Nonwhites showed the geographic variations in cancer by state economic area (a county or group of counties having similar social and economic characteristics). State economic areas were used in the *Atlas of Cancer Mortality* among whites to map the less common cancers.

To compare cancer rates among whites, blacks, American Indians, Chinese and Japanese, the NCI scientists also tabulated national death rates for each race. Compared to other nonwhites, blacks experienced high rates for cancers of the mouth and throat, esophagus, stomach, pancreas, larynx, lung, bladder and cervix, and multiple myeloma (a lymph cancer). American Indians experienced more cancers of the gallbladder, bile ducts and liver; Chinese had high rates for cancers of the nasopharynx (inner passages of the nose); and Japanese had increased stomach cancer rates.

(more)

CANCER (CONT'D)

The scientists have cautioned that to interpret the cancer patterns among nonwhites accurately, one must be aware of the uneven distribution of nonwhites across the U.S. They have included in the *Atlas* maps showing the distribution of all nonwhites in the U.S. in 1960, and race-specific county maps available for the first time from the 1970 census. The race-specific maps showed blacks living primarily in the South and in urban areas of the Northeast and Midwest. American Indians were primarily in rural areas of the Central and Mountain States, and Japanese and Chinese were predominantly in urban areas of the West.

In addition, the authors point out that many state economic areas had small populations of nonwhites during the 20-year period of the study. Consequently, apparently unusually high cancer rates among nonwhites, particularly in Central and Western areas, may reflect the small populations on which the rate is based.

Single copies of the *Atlas of Cancer Mortality Among U.S. Nonwhites: 1950-1969* are available free of charge from the Office of Cancer Communications, National Cancer Institute, Bethesda, Maryland 20014.

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NEWS & FEATURES From NIH

January 1977

Photo Feature

FIBROBLASTS SEEN TO FUNCTION IN MAINTENANCE OF PERIODONTAL LIGAMENT

Recent research from the State University of New York at Stony Brook supports the concept that fibroblasts are responsible not only for the synthesis of collagen but also for orderly removal of nonfunctional collagen in the periodontal ligament.

The synthesis and resorption of collagen are important processes in maintenance of the periodontal ligament. The ligament holds teeth in their sockets and cushions the jawbones from the stresses of chewing and biting.

For years scientists have known that fibroblasts secrete the long collagen molecules which twist together outside the cell to form fibrils that give skin, bone, and other connective tissues their toughness. Up until this time it was thought that the enzyme collagenase was the sole agent for degradation of collagen fibrils, and that the process occurred outside of the cells. The new findings show that collagen also is degraded within the cells.

Supported by NIH's National Institute of Dental Research, Philias R. Garant, D.M.D., confirmed recent electron microscopic findings of mature, banded collagen fibrils within fibroblasts. Dr. Garant postulates that tongues of cytoplasm called pseudopodia, which fibroblasts often extend beyond the main cell, can surround loose collagen fibrils. The cells can then pull the pseudopodia with their loads of collagen back into the cell body. It is known that fibroblasts contain contractile proteins which could enable them to extend and retract pseudopodia.

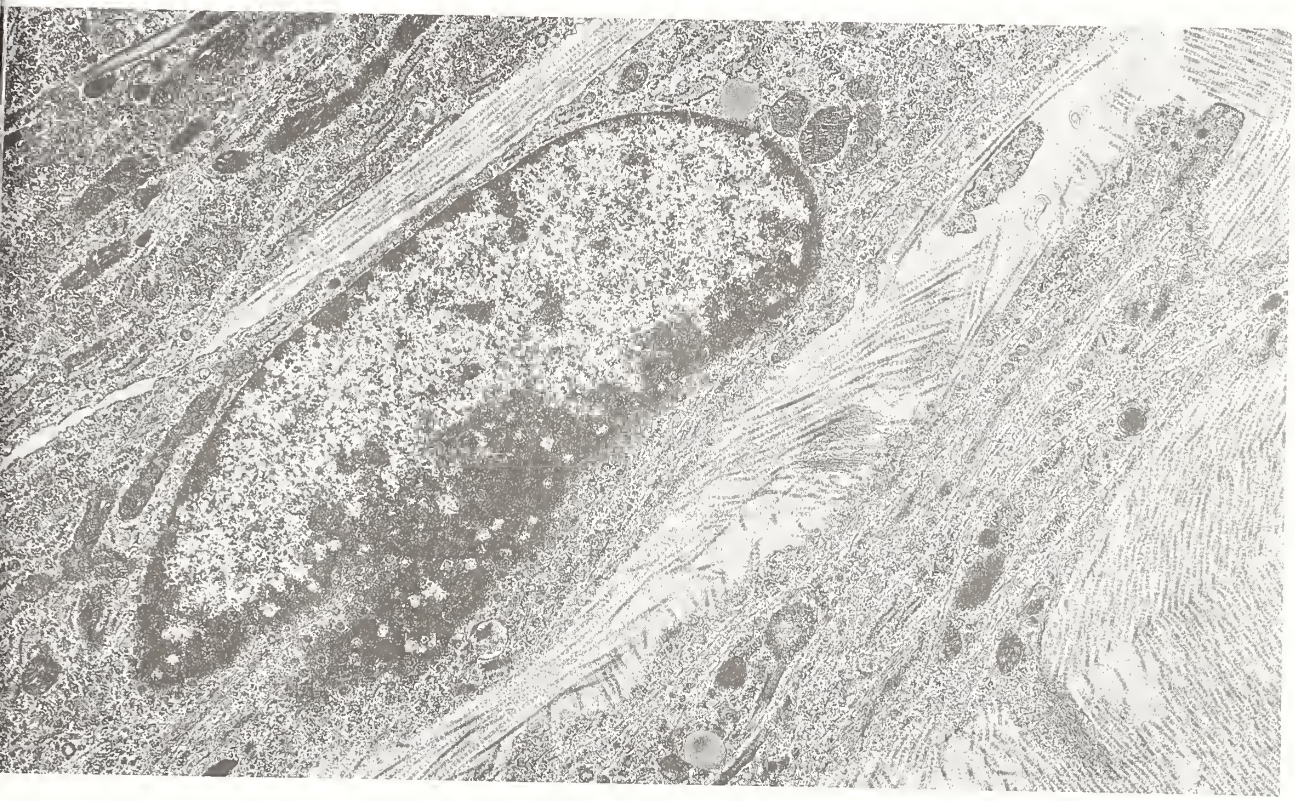
In addition, Dr. Garant described two functional compartments within fibroblasts. The slender, type A, compartment located near the cell's edge often contained banded collagen fibrils which sometimes appeared to lie half in and half outside the compartment. Type B, a rounder compartment, located

(more)

deeper inside the cell, contained dark masses of what appeared to be lysosomal protein-destroying enzymes. Sometimes the two types of compartments were continuous. Therefore, Dr. Garant believes that fibroblasts have both a way to gather collagen fibrils and to move them to the interior of the cell where they are broken down.

It appears reasonable that fibroblasts not only produce newly-synthesized collagen molecules, but also retrieve collagen fibrils disrupted by chewing forces, bone remodeling, or tooth eruption. Thus this cell could help to maintain the normal integrity of the periodontal ligament.

This research was reported in the *Journal of Periodontology*.



This is an electron micrograph of periodontal ligament fibroblasts. (NIH Photo #1577)

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Photo Feature

MORMON GENEALOGY RECORDS USED TO STUDY GENETIC ROLE IN ILLNESS

Mormon Church genealogy records are being computerized at the University of Utah Medical Center in Salt Lake City to study the role family history may play in serious illness. Eventually, the information could help in the prevention and early detection of cancer and other diseases, according to Dr. Homer Warner of the University's Medical Biophysics and Computing Department.

Using a CDC 3300 computer funded by NIH's Division of Research Resources, a group of investigators headed by Dr. Mark Skolnick, a population geneticist, will link the genealogy of 250,000 Mormon families with medical records to test several genetic hypotheses related to disease. Dr. Warner, a Mormon church official, calls the genealogy records "a unique data base that makes up the most detailed family relationship records in the United States."

The Utah researchers, funded by a National Cancer Institute grant, will determine first whether cancer runs in families. If a strong family relationship is confirmed, they will search for distinguishing traits of cancer-prone families. Dr. Warner eventually hopes to find a relationship between certain genetic markers--such as fingerprints--and cancer. He envisions quantifying these genetic markers for computer use so they can help identify high risk individuals within these families.

Dr. Warner explains that medical authorities now believe certain types of cancer run in families. "If a family at risk can be identified, then it might be possible to identify individuals within that family who have traits corresponding to genes which might predispose them to cancer," he says. "By identifying these people early, we can expose them to unusual detection

(more)

GENEALOGY (CONT'D)

efforts that would be cost-prohibitive to carry out for the entire population. With such thorough testing, we should be able to identify many lesions before they become malignant.

"We also can improve cancer prevention by counseling these people on environmental dangers--such as poor diet and smoking--which may trigger the start of cancer."

Dr. Skolnick already has used family relationships to determine individuals at high risk of contracting Wilson's disease, a neurological disorder which can result in the destruction of the liver. Utah researchers also plan to apply this approach to coronary heart disease, cerebral vascular disease, and "the whole spectrum of illness."

For right now, however, the study is concentrating on translating the Mormon Church genealogy records into computer usable language.

"Each Mormon is encouraged by the church to fill out a four-generation family chart which is kept by the Genealogical Society in the Mormon Church Office Building here in Salt Lake City," Dr. Warner explains. "Research assistants photocopy the family charts and bring the copies to nearby Latter Day Saints Hospital where the information is entered into the computer. With this data, the computer will reconstruct a detailed family history of the entire Mormon Church population in Utah.

"We hope to link this history to hospital medical records, death records, and the state's cancer registry to gain an insight into the role genetics plays in cancer etiology. From here, it should be possible to search the medical file for all patients having any particular disease and then locate these same patients in the genealogical files to determine interrelationships. This will provide an invaluable resource for genetic research, not only for

(more)

investigators at this institution, but all over the world."

The Utah team has been cataloging the genealogy files for more than two years. In another year, the investigators hope to begin linking the family history information with the medical data.

Dr. Warner emphasizes that the privacy of each individual will be scrupulously protected. It will be impossible to identify actual people from the computer records, he says.

"The heart of this effort is the computer hardware," Dr. Warner says while sitting behind his desk which has a computer terminal to his immediate left. "We couldn't do the work without the hardware, but of even more importance is the personnel we've been able to assemble because of the availability of our equipment through a grant from the Division of Research Resources at NIH."

Dr. Warner's equipment is funded through the Biotechnology Resources Program of the Division of Research Resources. The Biotechnology Resources Program conceives, develops, and assures the availability of resources that concentrate on the application of the physical sciences, mathematics, and engineering to biology and medicine.

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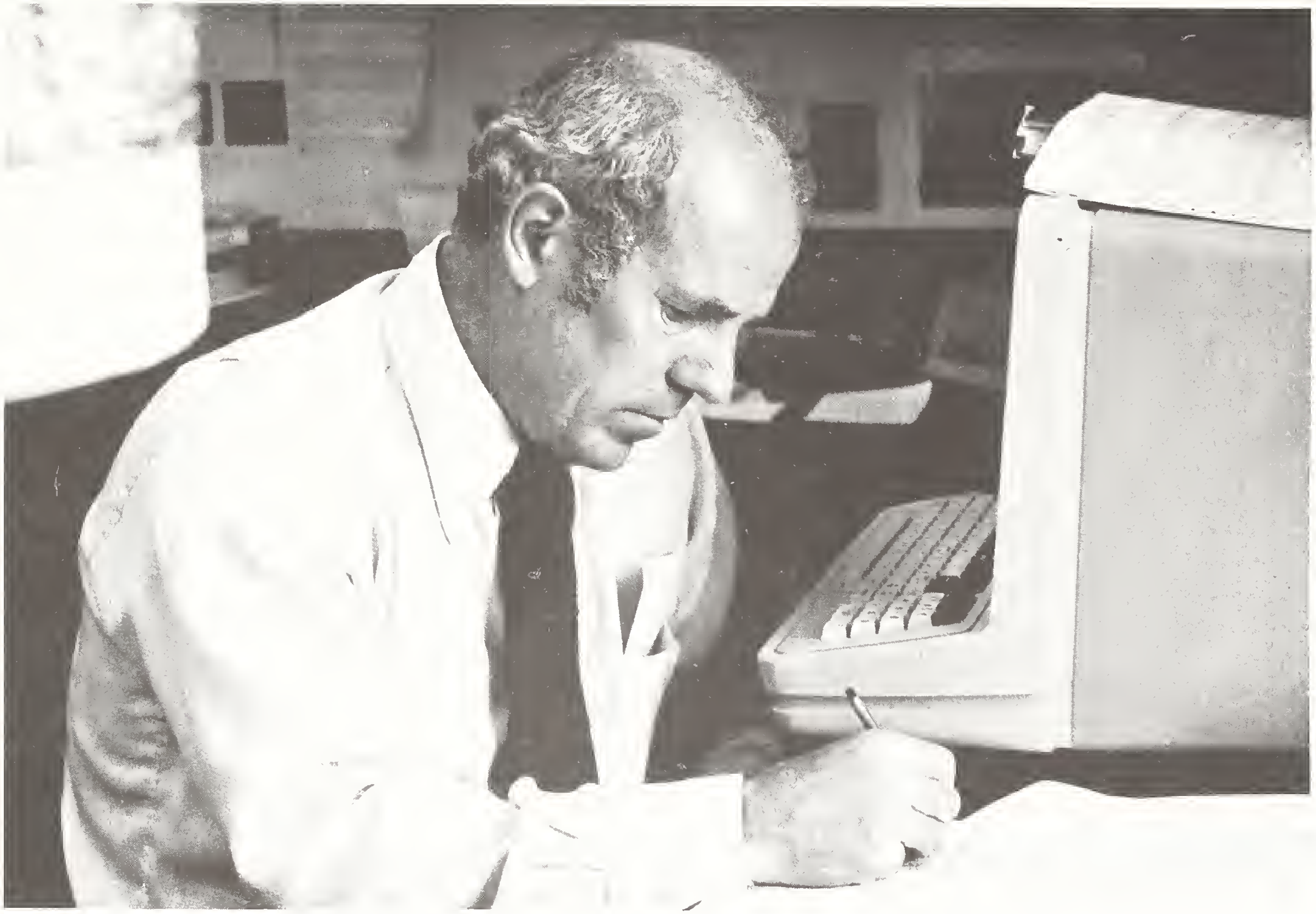
GENEALOGY (CONT'D)



Dr. Homer Warner checks a computer printout in his office at University of Utah-affiliated Latter Day Saints Hospital, Salt Lake City. Using computer facilities funded by NIH's Division of Research Resources, Dr. Warner is leading an effort which will computerize the genealogy records of the Mormon Church in Utah and link this information with medical records from throughout the state. Dr. Warner and his colleagues hope to determine if there are family relationships in certain types of cancer and other diseases, and if high risk individuals can be identified early. (NIH Photo #1578)

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NEWS & FEATURES From NIH

January 1977

News Feature

AMANTADINE HYDROCHLORIDE REDUCES VIRAL INFECTION

During an epidemic of the Hong Kong flu in 1968, amantadine hydrochloride, a proven antiviral drug, was administered in a controlled study and found to significantly reduce infection and illness among an unvaccinated population. This finding, by grantees of the National Institute of Allergy and Infectious Diseases (NIAID) supports other evidence that amantadine offers protection against influenza A viruses, the group of viruses responsible for most flu epidemics including "swine flu".

Every ten years or so, a new influenza A virus, with different antigens produces a world-wide epidemic. The virus responsible for the Hong Kong flu epidemic was just such a deviant, as is the virus called "swine flu". Most people have no immunity to a new virus, and when it appears, it often does so quickly and unexpectedly, leaving little time for mass production and distribution of a new vaccine.

In the event of an epidemic, one approach to protecting an unvaccinated or inadequately vaccinated population would be to administer a fast-acting, protective drug, or chemoprophylactic (in this case, amantadine hydrochloride) before exposure to infection.

Amantadine hydrochloride has been largely used to control the symptoms of Parkinson's disease, but its antiviral properties have been recognized for some time. Its precise mode of action is still unknown, but it probably either prevents entry of the virus into the cell or prohibits growth of the new virus.

In the reported study, the scientists tested the effectiveness of amantadine hydrochloride against influenza A on 105 college-age, unvaccinated students, 85 percent of whom had no detectable immunity against the newly emerged

(more)

AMANTADINE (CONT'D)

influenza virus. The students were divided into two groups, treated and untreated, and were followed for three separate periods, lasting 18, 16, and ten days. The treated group received oral amantadine twice daily during the first period, then alternated with the untreated group for the third period. When the students left campus during the second period, neither group received treatment.

During the two treatment periods, daily symptoms of respiratory disease were recorded. Before and after each period, serum samples were taken to determine antibody response, and thus, infection. A respiratory illness was classified as influenza when a four-fold rise in specific serum antibody was noticed.

The researchers found that when amantadine was given, influenza antibody levels were reduced by 64 percent among those who became infected. They also found that the number of students infected was reduced. While receiving amantadine, during either treatment period, nine percent of the susceptible students became infected with only three out of 90 actually developing symptoms. Among those who were not treated, 17 percent of the susceptible students became infected and ten out of 88 became ill.

The study also confirmed the fact that amantadine's protection ceases when the drug is discontinued. When neither group received amantadine, the previously treated group came down with a significantly greater number of infections than the untreated group. Based on this result, the researchers suggest that when vaccine is not available, amantadine be continued until influenza is no longer prevalent, often four to six weeks from the start of the epidemic.

(more)

AMANTADINE (CONT'D)

Although relatively non-toxic, amantadine hydrochloride can cause undesirable side effects, affecting the central nervous system, when used for long periods of time. To avoid these effects and to optimize protection, the researchers emphasize the importance of combining amantadine with a vaccine, continuing the drug for two to three weeks after vaccination. Previous studies have shown that amantadine increases the prophylactic effect of antibodies produced by a vaccine.

The results of this investigation agree with a number of other studies suggesting that amantadine provides about 60 percent protection against illness and 50 percent against infection. However, amantadine is only effective against type A influenza viruses, having no effect against influenza B viruses, a cause of milder flu infections.

The U.S. Food and Drug Administration recently licensed the use of amantadine hydrochloride for prevention and symptomatic management of infection with all influenza A viruses, making it available on a prescription basis. If a serious outbreak of swine flu strikes this winter, amantadine may once agains prove its effectiveness as a back-up measure in preventing infection from influenza A viruses.

The report of this research by Robert L. Mouldoon, Edith D. Stanley and George Gee Jackson from the Abraham Lincoln School of Medicine, University of Illinois and the Hektoen Institute for Medical Research of Cook County Hospital, Chicago, Illinois, appeared in the April 1976 issue of the *American Review of Respiratory Disease.*

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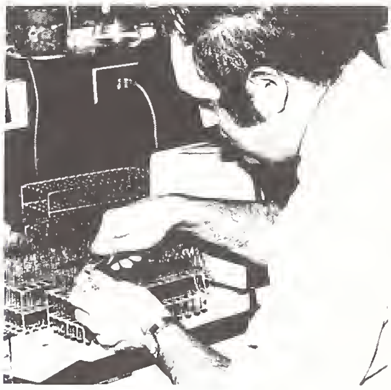

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February 1977

NEWS & FEATURES From NIH

Research Advances

POSSIBLE NEW MARKER FOR ALCOHOLISM IS RECOGNIZED

A grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has shown that the plasma alpha-amino-n-butyric acid to leucine ratio increases in relation to long-term alcohol consumption, and thus may become an objective empirical marker for the detection and assessment of alcoholism.

Alcoholism has been defined by many criteria, but a universally accepted or practical definition is not available. A biochemical marker of long-term heavy drinking, therefore, would enable objective evaluation of different treatment modalities for alcoholism, and provide a means for early detection and treatment of alcoholism.

The present research indicates that the ratio of plasma alpha-amino-n-butyric acid to leucine (A/L) is abnormally elevated in alcoholic individuals, and that this amino acid abnormality can be utilized as an objective empirical marker of alcoholism. The A/L ratio correlates well with the degree of alcoholism determined by established criteria in an active alcoholic population, and it can identify the majority of alcoholics within that population.

Plasma ratios of A/L were determined by analyzing blood samples obtained from 42 hospitalized alcoholics, 20 control subjects, and 19 patients with non-alcoholic liver disease. The mean A/L ratio in alcoholic subjects was more than twice that of non-alcoholic control subjects. It was shown that these abnormal A/L ratios are *not* dependent on the presence of alcohol in the blood, and that valid measurements can be made for a week or more after cessation of drinking.

Subsequently, the A/L ratio was investigated in 25 patients participating

(more)

ALCOHOLISM (CONT'D)

in a methadone maintenance program in whom alcohol and previous narcotic abuse were the only significant medical problems. Each subject was first assessed for alcoholism by three separate medical and psychological criteria employed by the National Council on Alcoholism (NCA). A statistically significant positive correlation was observed between the plasma A/L ratio and the degree of alcoholism assessed by each of the three NCA criteria.

Simultaneous studies in baboon revealed that these animals also develop abnormal A/L ratios when fed alcohol for prolonged periods, whether or not they are maintanined on an adequate diet. The mechanism whereby long-term alcohol consumption results in plasma amino acid abnormalities is not as yet known. NIAMDD grantee Dr. Charles S. Lieber of the Mt. Sinai School of Medicine and associates reported their findings in *Science*, Vol. 194, No. 4269, pp. 1057-1058, December 3, 1976.

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Research Advances

ANTIBODY GENES SEEM TO EVOLVE AS BODY MATURES

Workers at NIH's National Institute of Child Health and Human Development (NICHD) have been investigating the mechanism by which the immune system is able to generate the million or so distinct antibody molecules required in the body's defense against infectious disease.

Philip Leder, M.D. described studies in the Laboratory of Molecular Genetics, NICHD and other laboratories that seem to indicate that very unusual genetic mechanisms are involved in producing the vast repertoire of antibody molecules. The findings suggest that--unlike most of the body's genes which have evolved through evolution alone--antibody genes continue to evolve as the body matures. He spoke at an NIH Science Writers Seminar on January 25, 1977.

In order to fully understand this mechanism, investigators are now attempting to isolate the genetic elements responsible for antibody production, a task comparable to finding a needle in a very large haystack. However, new recombinant DNA technology, which permits the joining of genetic elements from different organisms, provides a very powerful and effective tool for this purpose.

Inasmuch as scientists have recognized that experiments involving the joining of genetic material from different organisms should be carried out with appropriate safeguards, these investigators have developed bacterial virus vectors which are a hundred-million fold reduced in their ability to survive in nature. Such vectors, in this case the bacterial virus called lambda, have been subject to a series of exhaustive tests and on the basis of

(more)

ANTIBODY (CONT')

these tests have been recommended for certification by the NIH Recombinant DNA Molecule Program Advisory Committee. They provide a means for studying this and other genetic systems vital to higher forms of life.

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CHOLESTEROL--Cholesterol, a fatty alcohol, or sterol, is found in all animal tissues and is especially abundant in the fat and fatty products of milk, eggs,and organ meats. There is none in vegetables or their native fats and oils. The average American diet supplies some 500-700 milligrams per day. The rest of the cholesterol in the blood is made in the body, mostly by the liver , according to the National Institutes of Health.

Research Advances

NHLBI INVESTIGATES ROLE OF GENES IN HEMOGLOBIN

Current research on the genes for hemoglobin, conducted at the NIH and elsewhere, was described January 25, 1977, by Arthur W. Nienhuis, M.D. of the NIH's National Heart, Lung, and Blood Institute, who related the hemoglobin studies to the thalassemias, the major group of single-gene defect diseases known. He spoke at an NIH Science Writers Seminar.

Hemoglobin, the molecule that carries oxygen in blood, normally contains two proteins: alpha- and beta-globin. The analogous fetal hemoglobin, normally present only in intra-uterine life, contains alpha-globin but has gamma- instead of beta-globin.

Recent studies at NIH by Albert Deisseroth, M.D., Ph.D., Ramon Velez, M.D. and Dr. Nienhuis have provided evidence that the alpha- and beta-globin genes are located on separate chromosomes. It is also known from analysis of certain hemoglobin variants that beta- and gamma-globin genes are genetically linked in humans; that is, the genes are close together in the DNA strand of a particular chromosome. Gamma- and beta-globin genes in humans and in other animals are expressed at different times during development, and thus may serve as a model for understanding the mechanism of regulation of closely related genes in the cells of higher organisms.

Studies by Robert Williamson, Ph.D. and colleagues at the Beatson Institute for Cancer Research in Glasgow, and research findings at the NIH by Edward Benz, Jr., M.D., Dr. Nienhuis, and co-workers indicate that regulation of these genes occurs at the time of RNA synthesis (transcription). Thus, in adult red blood cells, the beta-globin gene supports the production of beta-

(more)

globin messenger RNA, but the gamma-globin gene, although present in the same DNA strand, is not ordinarily transcribed into gamma-globin. Since the DNA strands exist in a chromatin structure, regulation appears to be imposed by some component, possibly a non-histone protein, present in chromatin.

George Stammatoyannopoulos, M.D. and colleagues at the University of Washington School of Medicine, Seattle, and independently Jane E. Barker, Ph.D., W. French Anderson, M.D., Dr. Nienhuis and other associates at the National Heart, Lung, and Blood Institute have devised a means of growing red blood cells that express these globin genes. Activation of the gamma-globin gene in laboratory-grown human cells and an analogous globin gene in sheep cells has been achieved, opening the way to test the effect of various substances on switching on and off the genes for hemoglobin. After incubation of the cells with a high level of the natural hormone erythropoietin, the mature globin genes have been effectively switched to a more immature globin gene by these laboratories.

Dr. Nienhuis observed that the often fatal human genetic disease, homozygous beta thalassemia (Cooley's anemia) is the direct result of a newborn infant's failure to synthesize the beta-globin component normally present in the hemoglobin molecule after birth. (Inadequate beta globin production leads to a relative excess of alpha globin which results in a decreased lifetime of red blood cells.) Studies conducted at the Beatson Institute, Yale University, University of California at San Francisco, Harvard University, and at the NIH have shown that DNA obtained from the cells of most patients with this disorder contains the gene for beta globin. Failure to synthesize this protein,

(more)

therefore, is believed due to an abnormality in the production and/or function of its messenger RNA (mRNA).

Recent studies at the Clinical Center of the NIH have shown that in certain patients the mRNA (transcribed from the beta-globin gene) is produced but that it does not accumulate in the normal fashion. Studies in another group of patients at the University of California in San Francisco by Y.W. Kan and associates indicate that the beta-globin messenger may be present in nearly normal quantities but no beta globin is made.

Activation of the gamma-globin gene to switch on its gene product could be an approach to treatment of Cooley's anemia, because gamma globin is an effective substitute for beta globin even during adult life.

Recent laboratory successes in achieving this goal offer hope that it may be possible in the future to achieve the same objective clinically, although there is no immediate prospect of doing so. For the moment, the findings underscore the importance of understanding the regulation of these human genes, and highlight the significance of molecular biology in clinical problems.

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Research Advances

"LIMITLESS" ANTIGENIC STIMULI CAN AFFECT HUMAN IMMUNE SYSTEM

The immune system must respond to a virtually limitless array of antigenic stimuli. This response involves the production of about a million different antibody molecules, each directed against a highly specific set of antigens. Chemical and structural studies over the past decade have indicated that this class of important molecules exhibits certain unique structural features that play an important part in the antibody-antigen interaction. This subject was discussed at an NIH Science Writers Seminar on January 25

As a rule, members of a given class of antibody molecules will have identical amino acid sequences in their constant regions, but differ from one another in their initial hundred or so amino acids, called the variable region. It is in this initial, diverse portion of the antibody molecule that the antibody binding site resides and alterations in its primary structure provide the enormous diversity and specificity which characterize antibody molecules.

A major problem in understanding the immune response has been to understand how this diversity arose and how it can be encoded in the organism's genome. A wide range of studies conducted over the past four years in our own and other laboratories now suggest that immunoglobulin molecules are encoded in a very small group of genes. The results furthermore suggest that constant and variable regions are separately encoded and come together during differentiation to form a continuous genetic sequence encoding an antibody subunit. The diversity which characterizes antibody molecules arises only in part through evolution, but appears to be completed during the process of differentiation of the antibody-producing cell.

(more)

ANTIGENIC STIMULI (CONT'D)

These conclusions require us to postulate two very unusual steps in the differentiation of antibody-producing cells. The first is a highly specific recombination mechanism for the joining of constant and variable region genes. The second is an unprecedented mechanism which would bring about mutations in a very highly restricted portion of the genome during the process of somatic development. This latter mechanism would be responsible for generating the final degree of diversity required to produce a complete repertoire of antibody molecules.

In order to understand the molecular mechanism responsible for bringing about these unusual reactions and to understand how one or another antibody sequence may be selected for production by an immunocyte, it is necessary to isolate and to obtain substantial amounts of gene sequences corresponding to immunoglobulin molecules.

In the course of the last few years, a new technology has been developed in a variety of laboratories (not our own) which makes the isolation and amplification of specific gene sequences feasible. Recombinant DNA technology should allow the cloning of a specific sequence corresponding to an immunoglobulin gene and thereby permit its isolation as well as its production in amounts necessary for biochemical experiments.

In an effort to clone these genes we have prepared and modified several vectors based on the bacteriophage lambda (λ) which we feel meet the requirements of a safe host-vector system necessary for cloning experiments involving mammalian DNA. These vectors provide several important advantages as regards safety and convenience which make them useful both for this and other important basic questions and practical applications involving the use of DNA from higher

(more)

organisms. Our current efforts are directed toward cloning the unusual genetic regions responsible for immunoglobulin production.

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TRIGLYCERIDES--Triglycerides are neutral fat esters and the predominant lipid of adipose tissue as well as the predominant dietary lipid. The average American diet provides about a gram of triglyceride per pound of body weight daily, according to the National Institutes of Health.

Research Advances

STRUCTURE, ACTIVITY OF CHROMATIN ARE DISCUSSED

Recent information about the structure and activity of chromatin, a combination of DNA (the genetic chemical deoxyribonucleic acid) and associated proteins (chiefly the group of proteins called histones) was described January 25, 1977, at an NIH Science Writers Seminar as resulting from several many-faceted research efforts on an international scale.

Gary Felsenfeld, Ph.D., a biochemist at NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases, discussed the work of scientists at many research centers, including Flinders University of Southern Australia; Cambridge University in England; and, in the U.S., at Oak Ridge National Laboratory, Oregon State and Princeton Universities, and at the NIH. He noted that they have forged strong evidence supporting the postulated "beads on a string" structure of chromatin.

Chromatin's structure is of significance insofar as the structure controls DNA's ability to be expressed, for example, in the differentiation of body cells into unique cell types, and in the production of necessary protein products such as hormones and enzymes.

The "beads on a string" structure, as proposed by the international scientific groups working independently, would facilitate the packing of incredibly large amounts of genetic information into the cell nucleus. Associated histones have been found to help create the bead-like structure. The question of what role they may play in masking and unmasking portions of the DNA is under investigation.

Each chromatin "bead" is described as consisting of a cluster of eight

(more)

histone molecules with a short length of DNA warpped around it. The beads are regularly spaced on the "string," a short length of DNA relatively free of protein. The configuration has been visualized with surprising clarity under the electron microscope by A.L. Olins and D.E. Olins of the Oak Ridge National Laboratory.

The recent reports on chromatin structure are of great interest because it is believed that the structure of chromatin is intimately connected with the control of cellular growth and differentiation. The latter is a central, unanswered question in the biology of higher organisms.

Five kinds of histones have been identified--H1, H2a, H2b, H3, and H4. Of these, two argenine-rich histones, H3 and H4, (together with DNA) have been reported to play a central role in the structure of the "bead." (See Barbara ✓ Sollner-Webb, Rafael D. Camerini-Otero, and Gary Felsenfeld, Chromatin Structure as probed by nucleases and proteases: evidence for the central role of histones H3 and H4, *Cell*, September, 1976.

#

Research Advances

SOME ADVANTAGES NOTED IN "SELECTIVE" SHUNT SURGERY

A Georgia grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has shown that the frequency of post-shunt encephalopathy is impressively less in patients who undergo "selective" rather than "total" shunt surgery for bleeding esophageal varices due to portal hypertension.

Cirrhosis of the liver is frequently complicated by portal hypertension and subsequent formation of esophageal varices, which may rupture and cause massive blood loss. Emergency surgery, usually in the form of a "total" shunt, may be performed as a last resort to control the bleeding. Such surgery, however, has a high mortality risk, does not increase longevity, and often leads to hepatic encephalopathy.

A randomized, controlled trial involving 48 patients has now demonstrated that a new surgical approach, the distal "selective" splenorenal shunt, is superior to the total shunt in several respects. Although mortality rates were similar regardless of the technique used, selective shunt therapy was associated with significantly less post-shunt encephalopathy, with preservation of portal blood flow, and with less deterioration of liver function.

The selective shunt (variceal decompression) was performed in 22 patients and the total shunt (portal decompression) in 26 patients. All 48 patients had biopsy-documented cirrhosis and were bleeding from esophageal varices. The prognostic value of a quantitative estimate of liver function, the maximum rate of urea synthesis, also was evaluated.

(more)

SHUNT SURGERY (CONT'D)

In the first two postsurgical years, fatalities numbered six in the selective shunt group and six in the total shunt group. Shunt occlusion occurred twice in each group and g.i. bleeding recurred three times in each group. Encephalopathy, however, developed in ten patients after a total shunt, but in only one patient after a selective shunt. Deterioration of liver function, as determined by monitoring urea synthesis, also was greater in the total shunt group.

The lower rate of encephalopathy in the selective shunt group was attributed to the fact that this procedure does not decrease portal flow to the liver. The data also suggest that the risk of post-shunt encephalopathy can be reduced by selecting patients for shunt surgery on the basis of a preoperative quantitative assessment of liver function, such as the maximum rate of urea synthesis.

NIAMDD grantee Dr. W. Dean Warren of the Emory University School of Medicine and associates reported their findings in the *New England Journal of Medicine*, November 11, 1976.

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News Feature

"CONGESTIVE" HEART FAILURE IS DESCRIBED BY NIH BOOKLET

Heart failure is very often "congestive", meaning either or both main pumping chambers (ventricles) are not emptying adequately during their contractions. This reduces the output of the heart, and increases pressure in the upper receiving chambers (atria) that receive blood from the great veins.

In left ventricular failure, the increased pressure that develops in the left atrium backs up blood in the pulmonary veins that empty into this chamber. This causes circulatory "congestion" in the blood vessels of the lungs, impairing respiration and sometimes leading to the accumulation of fluid in the lungs (pulmonary edema) that may be life-threatening. In right ventricular failure, the increased pressure that develops in the right atrium backs up blood in the large veins (vena cavae) returning blood to the heart from all parts of the body. This causes distention of the veins and circulatory congestion in the liver, spleen, and other organs.

With the development of heart failure, excretion of sodium by the kidneys is markedly reduced, leading to fluid retention and waterlogged tissues (edema) that develop first in the extremities, and then may spread to other areas of the body.

In infants and children, the most common causes of heart failure are congenital defects of the heart or great vessels and heart-muscle inflammation (myocarditis) developing during acute episodes of rheumatic fever. Among adults, the most common are: untreated or inadequately controlled high blood pressure; coronary heart disease and such consequences as acute heart attacks; and permanent damage to one or more heart valves resulting from rheumatic

(more)

fever episodes experienced earlier in life. Failure of the right side of the heart is also a frequent complication of far-advanced chronic lung disorders, such as emphysema.

Other significant causes of congestive heart failure include: 1) bacterial or viral infections affecting the heart; 2) degenerative heart-muscle disorders, collectively called cardiomyopathies and often of unknown origin; 3) certain glandular disturbances, such as hyperthyroidism; 4) severe nutritional deficiencies; and 5) alcoholism or chronic exposure to chemical agents harmful to the heart.

Compensatory mechanisms that, for a time, may protect against the development of congestive heart failure include increased stimulation of the heart via the sympathetic nervous system, enlargement of the heart (dilation), or thickening of the muscular walls of its pumping chambers (hypertrophy). Dilation and/or hypertrophy can carry the overburdened heart only so far, beyond which they cease to help heart performance and begin to hinder it.

The first goal of treatment is to identify the underlying condition that is driving the heart toward failure, if possible. The second is to ease the strain of the patient's overburdened heart by limiting his physical activity. The third is to administer cardiac stimulants or other therapeutic interventions as needed to improve the flagging performance of the heart. And the fourth is to prevent or combat excessive sodium and fluid retention by restricting dietary sodium intake and/or administering diuretic drugs.

Digitalis is the drug of choice for improving the pumping performance of the failing heart. This it does by slowing heart rate and increasing the vigor and efficiency of heart-muscle contractions, so that more blood is expelled

(more)

per beat. Other heart stimulants include norepinephrine, a hormone produced by the adrenal glands and in sympathetic nerve endings; dopamine, the substance from which norepinephrine is synthesized in the body; and the pancreatic hormone glucagon, which, in addition to its own beneficial effects on heart-muscle contractility, also appears to work well in combination with digitalis. Research has shown drug combinations are more effective in achieving a desired therapeutic result than is possible with a single agent.

Diuretic drugs are used for relief of fluid retention and edema. These include such potent, fast-acting agents as furosemide or ethycrynic acid, usually employed against severe edema or pulmonary edema in hospitalized patients with congestive failure. Other milder agents, suitable for the ambulatory patient, control fluid retention while posing little threat of serious fluid or electrolyte disturbances, especially if the diet provides an ample intake of potassium.

Data from the Framingham Heart Study indicate that, among subjects aged 45-74 with any of three predisposing conditions (coronary heart disease, rheumatic heart disease, or high blood pressure) but no overt symptoms of congestive heart failure, it is possible to identify those at highest risk. It involves evaluation of such variables as heart enlargement, ECG evidence of left ventricular hypertrophy, blood pressure, pulse rate, vital capacity, diabetes, and age. From analysis of these factors, it is possible to identify a relatively small group (20 percent of the population at risk) that will account for more than half the cases of congestive heart failure developing within two years. The hope is that earlier identification of the asymptomatic but high-risk subject and the initiation of preventive measures before the

(more)

heart has exhausted its reserves may often avert failure and prolong the person's life.

The National Heart, Lung, and Blood Institute is currently evaluating nitroglycerin, the time-honored drug for the relief of angina pectoris. Nitroglycerin reduces heart work (and hence its need for oxygen). It may also improve the blood supply to the heart by dilating collateral vessels that detour blood around sites of coronary artery obstruction. Often used in conjunction with nitroglycerin are methoxamine or phenylephrine, which prevent the rise in heart rate and reduction in arterial blood pressure normally elicited by nitroglycerin alone.

Aortic balloon pumping is a circulatory-assist technique that reduces the workload of the heart while helping to sustain systemic blood pressure and an adequate blood supply to the coronary arteries. It involves passing a balloon, mounted on the tip of a catheter, into the descending portion of the aorta. The balloon is then inflated and deflated in synchrony with heartbeat. Inflated as the ventricle refills between contractions, the balloon helps to maintain systemic blood pressure and coronary artery perfusion. Deflated as the ventricle contracts, it enables the heart to eject blood against a reduced aortic pressure and thus reduces the cardiac workload.

Infusions of glucose, insulin, and potassium are used in combination to correct local electrolyte disturbances in ischemic (blood-deprived) heart muscle and to provide a source of energy that can be tapped despite an inadequate oxygen supply.

Ventricular aneurysms are a relatively uncommon, but very dangerous complication of some acute heart attacks. Damage resulting from the attack

(more)

"CONGESTIVE" HEART FAILURE (CONT'D)

may so weaken the wall of the ventricle that it balloons out, creating a flaccid, non-contractile sac that damps the force developed during ventricular contraction and reduces its output of blood. The aneurysm poses a double threat: it can kill by rupturing, or it can drive the heart into failure. Both threats can be countered by surgical removal of the aneurysm.

Identification of risk factors, control of symptoms, and the medical and surgical management of congestive heart failure has improved. As a result, many potential cases of heart failure are being prevented or indefinitely postponed by procedures for correcting or palliating congenital or acquired heart conditions that, left untreated, must eventually terminate in congestive heart failure.

Emphasizing the importance of this continuing research effort is the fact that, despite the advances of the past 25 years, congestive heart failure or complications of the condition still kill half its victims within five years after overt symptoms appear and was listed as the primary cause of death for some 15,000 Americans during 1973.

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Adapted by Joyce C. Flaherty from the NHLBI Fact Sheet 76-923 "Congestive Heart Failure"

February 1977

News Feature

SCIENTIST MAKES HYBRID CULTURE OF NORMAL AND MALIGNANT CELLS

When normal and malignant human cells are combined genetically in the laboratory, the resulting hybrid cell culture shows no sign of its cancerous heritage, a University of California, Irvine (UCI), researcher has reported.

Dr. Eric J. Stanbridge, assistant professor of medical microbiology at the UCI College of Medicine, is maintaining hybrid cell cultures that have remained free from malignancy for more than two years.

Such an extended suppression of malignancy as an inherited trait was previously unknown in hybrid cells, which are used to study the genetic and biochemical properties of cancer, with the hope that new cancer treatments eventually will be found.

"Our studies clearly demonstrate that malignancy behaves as a recessive trait in certain human cell hybrids," Dr. Stanbridge said. "Human cell hybrids also exhibit a degree of chromosomal stability that other kinds of hybrid systems lack, which corresponds to a longterm suppression of malignancy."

Hybrid cells that result from the fusion of normal cells with cancer cells are said to be "transformed" because they bear characteristics of both parent cells and may represent an intermediate step in the formation of the cancerous state.

Most transformed cells act somewhat like cancer cells in a laboratory culture, growing and multiplying indefinitely. When injected into a suitable host, however, a hybrid cell with its genetic material intact will not cause a tumor, indicating that it is non-malignant, Dr. Stanbridge said.

The stability of human hybrid systems may enable researchers to isolate

(more)

HYBRID CULTURE (CONT'D)

and study intermediate steps in the transition of a healthy normal cell to a malignant cancer cell, he said.

Genetically stable, non-malignant transformed cells someday might also prove useful as immunotherapeutic agents to stimulate the body's immune system to reject a tumor, he added.

The key to the lack of malignancy transformed cell is contained in the physical expression of the cell's genetic code. Genes--specific sites on the cell's chromosomes--consists of molecular codes that carry the cell's master plan and regulate chemical functions in the required sequence for cell growth, metabolism and division. If physical traits inherited through gene expression are dominant or co-dominant, they show up in the cell. Recessive traits, however, are suppressed and do not show up in the cell.

Widely studied hybrid cell systems created from normal and malignant mouse cells or combinations of mouse and human cells show an initial suppression of malignancy. During subsequent cell divisions, however, they lose some of their chromosomes and become malignant. Scientists believe this effect occurs when genes responsible for holding the cancer trait in check are lost.

Until Dr. Stanbridge's study it was generally assumed that chromosome loss and reversion to malignancy were characteristic of hybrid cell systems. Working exclusively with human cells, however, the UCI professor has created several relatively stable hybrid systems by fusion normal cells and single or combined malignant cells from three types of tumors--carcinoma, sarcoma and leukemia.

(more)

Dr. Stanbridge's work has been supported by grants from NIH's National Cancer Institute and the California division of the American Cancer Society. He also has received a research fellowship from the Leukemia Society of America.

#

LOW BIRTH WEIGHT--In the United States, low birth weight is the most important single factor linked to the high infant mortality rate, according to the National Institutes of Health.

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CONGENITAL MALFORMATIONS--In the United States in a single year, as many as 200,000 children will be born with one or more congenital anomalies. These malformations probably result from an interaction between genetic and environmental causes, according to the National Institutes of Health.

NEWS & FEATURES From NIH

February 1977

Photo Feature

PITTSBURGH DOCTORS DEVELOP TEST WHICH CAN DETECT HYPOTHYROIDISM

University of Pittsburgh doctors working at Children's Hospital of Pittsburgh and Magee Women's Hospital have developed a laboratory test which can accurately and economically screen for congenital hypothyroidism, a subtle and difficult-to-detect medical condition which can cause irreversible mental retardation in infants if not discovered and treated early.

The screening test was developed with the help of the Biomedical Research Support Grant Program of the National Institutes of Health's Division of Research Resources (DRR). By providing money to medical institutions based on a percentage of their existing Public Health Service grant support, these awards are meant to be used for pilot research projects, including the exploration of new ideas by young investigators.

According to Dr. Thomas P. Foley, Jr., who supervised the team that developed the new screening test, congenital hypothyroidism affects about one in every 5,000 newborns. Termed "cretinism," the problem involves insufficient synthesis of thyroid hormone. The symptoms are usually so obscure during infancy that the disease is not recognized and, therefore, early treatment is not started.

In 1974, using money awarded as a DRR Biomedical Research Support Grant, the Pittsburgh doctors discovered that congenital hypothyroidism could be detected by measuring the level of serum thyrotropin (TSH), a pituitary hormone that stimulates the thyroid gland to produce thyroid hormone. Originally, the doctors measured TSH levels in the serum of cord blood collected at birth. After additional research, they were able to modify the procedure so it could be incorporated into the existing phenylketonuria (PKU)

(more)

screening program, which is mandated by legislation in most states.

"We were able to detect congenital hypothyroidism by determining the TSH in cord serum," Dr. Foley reports. "The procedure provided us with a high index of discrimination and a low false positive rate, but it was very inconvenient to collect and process cord blood samples. . . and often they weren't collected at all in non-hospital births. For these reasons, we decided to incorporate the test into the PKU screening program. To accomplish this, we measured TSH in material washed from a six millimeter disc punched from filter paper to which a drop of blood from a heelprick had been applied during the third day of life.

"Later, we thought we could make the test even more convenient and cost effective by making it compatible with the fully automated laboratory systems which screen for several metabolic disorders in newborns. To do this, we began to measure TSH in material washed from three millimeter discs, using an automated radioimmunassay system which easily discriminates between affected and normal infants."

With the various modifications that the procedure has undergone, Dr. Foley believes it meets accepted criteria which make it clinically appropriate and worthwhile, including the ability to screen for a disease considered to be serious and having some general importance to the community, the ability to differentiate between affected and non-affected individuals with ease, the ability to diagnose a disease which can be detected by the test but is not apparent clinically, and the ability to conduct the test at a reasonable cost.

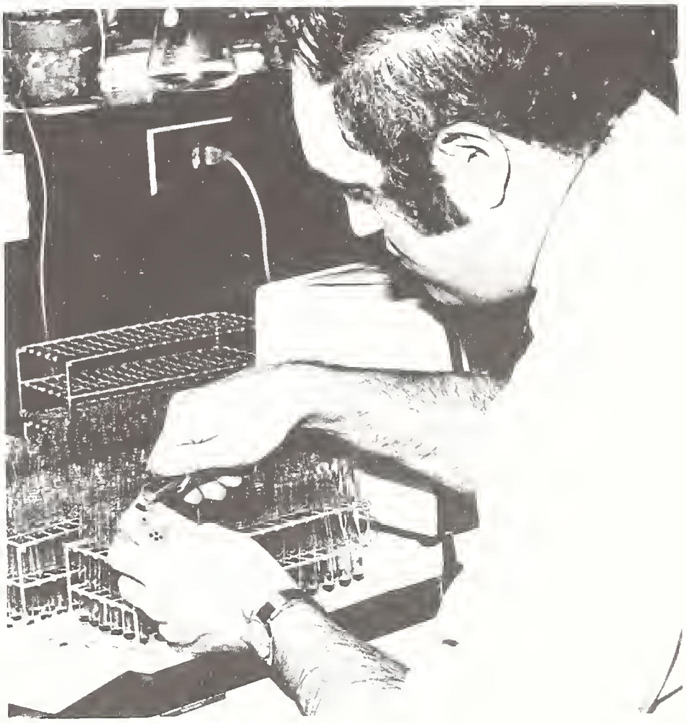
"We now can routinely detect congenital hypothyroidism so that those

(more)

HYPOTHYROIDISM (CONT'D)

affected can receive early treatment thereby reducing mental retardation caused by this disease," Dr. Foley says. "To date, we have detected eight infants with congenital hypothyroidism, started treatment at any early age, and found that all the infants subsequently have had normal growth and mental development.

"Initial support from the Biomedical Research Support Grant Program of DRR enabled us to begin our investigations into this problem and to eventually receive grant monies from other sources to expand the studies so we could find the best possible method for detecting this disease."



Dr. Thomas P. Foley, Jr., of the University of Pittsburgh, punches small discs from filter paper in preparation for newly developed screening test for hypothyroidism in newborns. A drop of blood from an infant's heelprick has been applied to the filter paper prior to punching out the three millimeter discs. The screening procedure was developed at the University of Pittsburgh with the help of a grant from the Biomedical Research Support Program of the Division of Research Resources, National Institutes of Health. By providing money to medical institutions based on a percentage of their existing Public Health Service grant support, these awards are meant to be used for pilot research projects, including the exploration of new ideas by young investigators. (NIH Photo #1579)

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News Feature

SPECIAL DRUG THERAPY APPEARS TO IMPROVE A KIDNEY DISORDER

A New York grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), in a long-term retrospective study of patients with idiopathic membranous nephropathy, has demonstrated that corticosteroid and/or immunosuppressant drug therapy is superior to no treatment. The scientists used the criteria of clinical improvement, recurrence rate, occurrence of renal failure, and mortality.

Idiopathic membranous nephropathy, a kidney disorder marked by proteinuria and lesions of the capillary wall, is often characterized by slow clinical progression or by episodes of spontaneous improvement and remission with occasional relapses. Although it is difficult to evaluate the effect of therapy in such a disease, it has been generally accepted that idiopathic membranous nephropathy is *not* responsive to corticosteroid or immunosuppressant drug therapy.

A long-term retrospective study of 103 patients with this disease now has described a favorable outcome in 59 who were treated, as compared to 44 who were not treated. Whereas clinical cure and improvement were significantly greater in untreated patients, the recurrence rate, occurrence of renal failure, and probability of death were significantly greater in untreated patients. The data suggest that corticosteroid drug therapy may be beneficial in patients with idiopathic membranous nephropathy.

Ninety-one adults and 12 children with biopsy-proved idiopathic membranous nephropathy were followed for periods up to 29 years (mean 6.5 years) after clinical onset of disease. Forty-four were treated with prednisone, and 15

(more)

with both prednisone and cyclophosphamide or azathioprine. Another 44 received no treatment and these patients served as "a built-in unplanned control group."

Remission of disease occurred in 17 treated patients, but in only two untreated patients. Similarly, renal failure and death in uremia occurred in 21 untreated patients, but in only nine treated patients. Overall, 31 of 44 patients treated with cortisone, and nine of 15 treated with cortisone and immunosuppressant drugs improved, while only 13 of 44 untreated patients showed any improvement.

The results of this study suggest that prognosis in membranous nephropathy is better in patients whose diagnosis is made early in the course of disease, and that adequate corticosteroid drug therapy (or possibly immunosuppressant drug therapy) may be beneficial, particularly in patients with lesser degrees of basement-membrane damage. NIAMDD grantee Dr. Jacob Churg of the Mt. Sinai School of Medicine and associates reported their findings in the *New England Journal of Medicine*.

#

News Feature

THE FLU IS MANKIND'S "LAST GREAT PLAGUE"

Flu, or influenza, is an acute respiratory illness whose symptoms include fever, cough, sore throat, a "runny" nose, and general muscular aches. Most patients recover completely within a week although many continue to feel unusually tired for some time. In the aged or the chronically ill, however, flu is a life-threatening illness. Together with pneumonia, it is the fifth leading cause of death in the United States.

Influenza is caused by a virus which, though identified by scientists as long ago as the 1930's, is still the subject of intensive research. The three types of influenza virus identified are called types A, B, and C. Increased knowledge of the chemical and molecular structure of the influenza virus and its behavior in animals and humans is expected to yield a better understanding of the disease itself and of means for preventing it.

Over the years scientists engaged in the most fundamental research have explored the genetic makeup of more than 100 respiratory viruses. They have found that, in general, these agents consist of a continuous strand of nucleic acid (RNA or DNA) on which are strung the genes which carry instructions for viral self-duplication.

The influenza virus is different. Its nucleic acid--RNA--consists of seven or eight discrete pieces, each of which controls a specific viral function. The nucleic acid is contained within a protein envelope which is studded with molecules of two major antigens--neuraminidase and hemagglutinin--which play an important role in the ability of the virus to attack and destroy cells.

The fragmented nature of the genetic material of the influenza virus is

(more)

believed now to account for the agent's unique and puzzling ability to undergo periodic changes which render available vaccines useless and vast populations vulnerable to attack.

The unpredictability of the flu has been recognized for centuries. In fact, in earlier times, the ferocious reappearance of the disease, after an absence of years, would lead observers to assume that a new plague had struck. During the past century alone, there have been seven instances of global spread, known as pandemics, and numerous epidemics, when the occurrence of influenza is more or less restricted to one region.

Outbreaks of flu usually occur abruptly. The disease spreads through communities, peaking in about three weeks and subsiding after another three to four weeks. Twenty to 50 percent of susceptible members of the population may be affected, with the highest incidence in children, ages five to 14.

"New" strains of influenza A virus cause pandemics, which occur approximately every 10 years. For example, in 1957, it was the Asian flu and in 1968, the Hong Kong. Although the viruses causing these outbreaks belong to the same class of influenza virus--type A--they differed significantly in one surface antigen--the hemagglutinin--and, hence, in the protective antibodies which this chemical invokes in the body.

Influenza caused by type B virus does occur in epidemic form, but the disease is generally milder than that caused by influenza virus A. Type C viruses have never been connected with a larger epidemic.

It has been shown that influenza A and B viruses change their genetic make-up slightly each year. These annual changes are known as "drifts". A major shift which occurs at approximately 10-year intervals has been observed

(more)

only for influenza A.

These genetic changes have posed a special problem for developers of vaccines. As the virus "drifts," immunity created by previous infection or vaccines becomes less effective. When a completely new virus strain appears, there has not been, in general, sufficient time between the recognition of the new strain and the beginning of a pandemic to produce the quantities of vaccine needed.

Studies in military groups, where vaccine administration is optimal and results can be easily monitored, have shown that present methods of producing influenza vaccines result in a product 70 to 90 percent protective, when matched to the current virus. Immunity, however, is not longlasting and annual revaccination is recommended.

Knowledge obtained in recent years is making it possible for scientists to develop experimental vaccines which should solve some of these problems. For example, laboratory studies have shown that if cells are infected simultaneously with two different influenza A virus strains, new viruses appear that may differ from both parents. These new viruses will have picked up some genes from one strain and some from the other. There is experimental evidence that this kind of recombination does occur in animals and birds as well as in the test tube.

Some scientists believe that use of this quirk of Nature may hold the key to providing protection against new virus strains as they appear in the population. Investigators have found that mating of a virulent virus with a less virulent strain usually results in a progeny virus that is suitably attenuated for use as a vaccine. It has been proposed that scientists could

(more)

draw on a parent "bank" of virus strains to custom-tailor hybrid vaccine strains to meet needs as they arise.

Such a recombinant killed vaccine, called X-31, has been developed and tested in military trainees. It was found that, during an influenza outbreak on the base, the rate of infection was four times greater in the unvaccinated group of recruits than among those who received the X-31 vaccine.

During the last few years, scientists at NIH's National Institute of Allergy and Infectious Diseases (NIAID) and investigators at other institutions have been manipulating the genetic material of influenza virus in ways that will alter or attenuate its virulence so it can be used as a live virus vaccine. For example, influenza virus strains have been altered so as to produce mutants which are "temperature-sensitive". These mutants will grow only in the cooler areas of the upper respiratory tract and not in the warmer, more delicate tissues of the lungs. Taking this process one step farther, scientists then mated these mutants with virulent strains of influenza virus and found that the attenuating, or temperature-sensitive, defect can indeed be transferred through recombination.

An experimental vaccine which induces the formation of antibodies against the surface antigen, neuraminidase, is also being evaluated. This represents another approach to the development of a live virus vaccine. The goal of such a vaccine is to provide partial immunity. Theoretically, when a vaccinee is later exposed to the natural virus, he would develop higher levels of protective antibody and achieve full immunity without developing symptoms of influenza.

Other developmental research is concerned with determining the best method of giving influenza vaccine. The exact mechanism of spread of the influenza

(more)

virus is not completely understood, but it is believed that, in general, the agent enters the body through the upper respiratory tract. Antibodies produced in that area, therefore, should be more protective than those induced in the circulating blood. Consequently, nose drops and sprays are being compared with the more conventional injections for efficacy in delivering doses of vaccine.

Vaccines are, of course, only preventive. They are of no value once the disease is under way. The usual advice of a physician is to go to bed, drink plenty of fluids, and take aspirin to relieve some of the uncomfortable symptoms of influenza.

Attempts are being made, however, to develop anti-influenzal drugs. The most promising of these, at this time, are amantadine and its derivatives. These and other anti-influenzal drugs may be useful both in treating the disease and in preventing it. Several inducers of interferon--a protective substance which occurs naturally in the body--have been initially promising but have produced side-effects which limit their usefulness.

The most frequent complication of flu is a secondary bacterial infection in the lower respiratory tract. Pneumococci are most commonly involved although staphylococci, streptococci, and *Hemophilus influenzae* may also cause pneumonia following or accompanying the flu. Usually these bacterial infections can be successfully treated with antibiotics. In recent years, however, drug-resistant pneumonias, especially among hospital patients, have been on the increase.

The National Institute of Allergy and Infectious Diseases has developed a comprehensive program of grant and contract-supported research on influenza.

(more)

THE FLU (CONT'D)

In addition, investigations are carried out in the Institute's laboratories on the grounds of the National Institutes of Health in Bethesda, Maryland. Acting on the advice of influenza experts who participated in a series of Institute-sponsored workshops, NIAID is encouraging investigation into the genetics, structure, and biology of influenza viruses.

Research continues on the development of new kinds of influenza vaccines. In addition to the temperature-sensitive mutants already mentioned, cold-adapted strains of influenza virus show promise as vaccines. In foreign countries, too--Great Britain, France, and Russia--investigators are pursuing various approaches to development of live vaccines.

For just as the flu itself is worldwide, so is the attack that has been launched against it. Only through such efforts will mankind's "last great plague" be conquered.

#

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March 1977

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March 1977

NEWS & FEATURES From NIH

Research Advances

NEW DRUG IS APPROVED FOR OCULAR HERPES SIMPLEX

A new drug, Vidarabine, was approved in January for the treatment of ocular herpes simplex virus, the most common cause of severe eye infection in the United States. The disease, which affects the cornea and iris, begins in childhood or during adolescence and frequently recurs, causing pain and visual disability throughout life. Idoxuridine (IDU), the only established treatment for herpes simplex keratitis, is generally effective, but its undesirable side effects have stimulated the search for new therapeutic agents.

Laboratory and clinical trials by Dr. Deborah Pavan-Langston and her associates at Harvard Medical School, Massachusetts Eye & Ear Infirmary, the Eye Research Institute of Retina Foundation, and Parke-Davis and Co., have demonstrated that vidarabine is effective for treating patients who cannot tolerate IDU or who develop IDU-resistant infections. This research was supported in part by NIH's National Eye Institute.

Herpes simplex virus infects about 80 percent of the population at least once a lifetime, usually causing cold sores, fever blisters or, in its more serious form, ulcerations of the genitals or scarring of the cornea and iris of the eye.

The 300,000 ocular herpes infections reported annually in the United States are caused primarily by Type I herpes, the same form of herpes that affects the mouth. When blindness occurs, the only way to restore vision is through corneal transplantation.

Until IDU became commercially available in the early 1960's, there were no drugs to treat ocular herpes. However, with increased use of IDU, more

(more)

OCULAR HERPES SIMPLEX (CONT'D)

patients developed such complications from the drug as allergic reactions and toxicity symptoms. In addition, doctors noted several herpes infections were resistant to IDU.

Vidarabine appears to avoid these untoward effects. Of 116 patients who had shown no improvement when treated with IDU, 78 percent healed when switched to vidarabine. Dr. Pavan-Langston also reported that vidarabine was as effective as IDU in treating 169 patients with routine ocular herpes infections. The drug was also of great use in treating recurrent herpes in 146 patients intolerant of or resistant to IDU. None of these patients suffered the significant toxic reactions usually seen with prolonged use of IDU.

In laboratory studies with rabbits, Dr. Pavan-Langston compared the toxic effects of IDU and vidarabine on experimental corneal wound healing. Her tests confirmed that vidarabine is less toxic than IDU. This suggests that vidarabine might be useful in treating herpes infections following corneal transplantation.

Vidarabine has been approved as safe and effective by the Food and Drug Administration. It is now available as a prescription ophthalmic ointment.

However, like IDU, vidarabine cannot treat deep-seated infections inside or behind the eye due to the drug's poor penetration of ocular tissues and its rapid conversion to inactive or less active metabolites.

Research on improved antiviral drugs to treat corneal infections is one of the highest priorities of the National Eye Institute. Studies are now underway to find drugs that can provide therapeutic access to deep-seated herpes infections. Nevertheless, vidarabine represents an important step in the improved treatment of ocular herpes simplex infections.

#

Research Advances

NIDR SCIENTISTS DEVELOP NEW STRAIN OF BACTERIA

A new "disarmed" strain of bacteria has been developed. It should help allay the fear that scientists transplanting genetic material from viruses and higher organisms to bacteria might accidentally release a dangerous new organism into an unsuspecting world.

In work partially supported by the National Institute of Dental Research, Dr. Roy Curtiss, III, of the University of Alabama'a Institute of Dental Research has succeeded in generating an organism which cannot survive in nature but can facilitate the study of "recombinant DNA." DNA is a very long molecule that contains the code for the production of specific proteins by any normal cell.

Today scientists have developed techniques for making new combinations of DNA molecules in the test tube, and this will eventually enable them to modify bacteria so that these cells can make enzymes now found only in animals or higher plants. Thus bacteria might supply a congenitally missing enzyme for a child who cannot digest milk. This mixing of genes across previously impenetrable barriers to hybridization is the basis of future recombinant DNA research.

Dr. Curtiss chose the K-12 strain of *Escherichia coli* as the parent organism because in the 55 years since it was isolated from a human it has been thoroughly studied, and is now less vigorous and more attenuated than wild *E. coli* which survives in soil, thrives in sewage, and normally inhabits human and animal intestines. With the help of eight colleagues, in the short course of about a year Dr. Curtiss has incorporated 15 different mutations into descendants of K-12. Now, after several more months of testing, they

(more)

capsule that protects many enteric bacteria from digestion, is still another imposed barrier to its normal life.

Moreover, Chi 1776 cannot make DAP (diaminopimelic acid), a necessary constituent of the rigid walls synthesized by most other Gram-negative bacteria. In nature, free DAP is scarce and in its absence Chi 1776 soon outgrows its cell wall and bursts.

Another handicap that Dr. Curtiss has introduced is sensitivity to sunlight. When its DNA is damaged by ultraviolet light, Chi 1776 cannot make repairs either in the dark or in visible light. Since sunlight contains ultraviolet rays, the organism would die in the air or on the ground.

Although thymidine is necessary to make DNA, Chi 1776 is dependent on the culture medium for this essential material. Dr. Curtiss notes that in nature there is little free thymidine, and when it is not provided by a bacteriologist, Chi 1776 tries to grow by using its own DNA as a source of thymidine, and thus destroys itself.

Many bacteria look like Chi 1776, and to prevent inadvertent contamination of experimental cultures with a wild-type organism that might live outside the laboratory after it had acquired some new, unwanted DNA, Dr. Curtiss has introduced two genes unknown in plasmids and very rare in wild-type *E. coli*. These genes give Chi 1776 resistance to nalidixic acid and to cycloserine, chemicals which kill most bacteria. To avoid mistakes, these chemicals are added to the culture medium before recombinant experiments are conducted.

There are other bars to the creation of unwanted, viable strains. Chi 1776 is resistant to most of the bacteriophages or viruses which can introduce

(more)

Dr. Roy Curtis III is shown inoculating a petrie dish with Chi 1776. (NIH Photo #1580)

(more)

BACTERIA (CONT'D)

Dr. Roy Curtis III is shown examining samples of his Chi 1776 cultures (NIH Photo #1581)

#

Research Advances

CIGARETTE SMOKING RAISES NOREPINEPHRINE LEVELS

Medical researchers have demonstrated that cigarette smoking stimulates the human sympathetic nervous system, providing a possible explanation for the two times higher heart attack rate among smokers as compared to non-smokers.

Using a special patient-centered research unit funded by the National Institutes of Health's Division of Research Resources, investigators at the Washington University School of Medicine in St. Louis have shown for the first time that blood levels of norepinephrine, a substance released by stimulated sympathetic nerves, are higher during smoking. The researchers said the substance is not released during sham smoking, leading them to the theory that the release of norephinephrine is smoking-induced.

The Washington University team carefully studied 10 volunteer patients on the University General Clinical Research Center, one of 82 such units supported by the NIH's Division of Research Resources at medical institutions throughout the United States. The Clinical Research Center is actually a miniature research hospital within the larger medical center, providing highly specialized clinical research facilities to the entire Washington University medical staff.

As part of the study, the research patients were treated with drugs which block the effects of norepinephrine. These effects include several physiological events associated with smoking, such as heightened blood pressure, increased heart rate, and high levels of blood glycerol. When these events did not take place in smoking patients after the administration of the norepinephrine-blocking drugs, the investigators deduced that cigarette smoking stimulates the sympathetic nervous system to produce norepinephrine which in turn brings

(more)

about these physiological effects.

"People who do not smoke, including former smokers who have given up the habit, have fewer heart attacks than those who continue to smoke," says Dr. Philip E. Cryer, associate director at the Washington University General Clinical Research Center. "Since sympathetic nerve stimulation has been shown to facilitate experimental heart attacks in animals, the observation that smoking stimulates the sympathetic nerves provides a plausible mechanism for smoking-associated heart attacks in humans. If this is so, it is theoretically possible that some of these heart attacks could be prevented by the administration of currently available medications which block the effects of norepinephrine."

The Washington University team reports that the Division of Research Resources-funded Clinical Research Center was instrumental in helping the investigators reach their findings. "Blood samples were obtained and blood pressures and pulse rates were measured and recorded at two and one-half minute intervals," Dr. Cryer explains. "Blood norepinephrine levels were measured in the special Core Laboratory of the General Clinical Research Center. These studies required research-trained nurses, sophisticated laboratories, and a totally controlled environment, all of which were readily available at the center."

#

Research Advances

NEW DRUG INHIBITS GASTRIC ACID SECRETION

Scientists supported by NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) have shown that the H_2-receptor antagonist, cimetidine, taken orally with an normal meal, safely and effectively inhibits gastric acid secretion without affecting other postprandial gastric, pancreatic, or biliary functions.

Previous NIAMDD-supported research has shown that the H_2-receptor antagonist, cimetidine, is a potent inhibitor of gastric acid secretion in patients with duodenal ulcer, and that it inhibits nocturnal gastric secretion safely and effectively in such patients. Gastric, pancreatic, and biliary responses to cimetidine after ingestion of an ordinary meal, however, have not been quantified heretofore in duodenal ulcer patients.

The present study has shown that cimetidine, taken orally with an ordinary meal, markedly inhibits gastric secretion without affecting gastric emptying and pancreatic and biliary function. This agent, therefore, should prove useful in the management of acid-peptic disease by achieving a postprandial gastric antisecretory effect without interfering with other digestive functions.

Following baseline studies, ten patients with active duodenal ulcer were given oral doses of 200 or 300 mg cimetidine, or placebo, in a randomized fashion while consuming an ordinary meal. For four hours thereafter, gastric and duodenal contents were sampled periodically via aspiration for continued measurement of gastric, pancreatic, and biliary secretory outputs. Periodic blood samples also were analyzed for cimetidine and gastrin concentrations.

Both the 200 and 300 mg doses of cimetidine significantly reduced postprandial gastric acid output and acid delivery into the duodenum. Acid inhibition

(more)

was related to blood cimetidine concentrations, which were higher after the 300 mg dose. Gastric secretory volume and pepsin output were less affected. As the stomach emptied the food, the gastric pH rose. The fractional gastric emptying rate, pancreatic enzyme, and bile acid outputs were unaltered.

Histamine H_2-receptor antagonists, such as cimetidine, are potentially useful agents in duodenal ulcer, and knowledge of their physiological effects on postprandial digestive events will contribute to their clinical application and usefulness. Because cimetidine is less potent postprandially than during nocturnal fasting, a higher dose or adjuvant therapy may be needed when the drug is given with meals.

Drs. George F. Longstreth, Vay L. W. Go and Juan-R. Malagelada of the Mayo Foundation reported their findings in *Gastroenterology*, Vol. 72, No. 1, January, 1977.

#

NEWS & FEATURES From NIH

March 1977

Photo Feature

TWINS SURVIVE OPEN-HEART SURGERY

Jane and Cathy D'Alessio -- 11-year-old twins with a rare blood type -- recently underwent open-heart surgery for repair of congenital defects at the Clinical Center, research hospital of the National Institutes of Health (NIH). The success of the surgery depended, in part, on NIH Blood Bank and American Red Cross efforts in collecting enough blood for the operations.

The girls, the second pair of twins in a family of nine children, were both born with a hole in the wall -- septum -- separating the upper chambers of their hearts. The chance of a baby being born with a congenital heart defect is about one in 200, but the probability of twins being born with such a defect is more remote. About 5,000 open-heart operations have been performed at NIH, but this is the first time surgeons here have seen the atrial septal defect in twins.

The defect in the atrial wall allows oxygenated blood from the left atrium or chamber to mix with unoxygenated blood in the right atrium. This greatly increases blood flow through the lungs, but circulation is impaired in other parts of the body, resulting in delayed growth and development. The twins weigh only about 45 pounds, whereas most 11-year-olds weigh about 75 pounds.

Twenty-eight pints of Jane and Cathy's blood type -- AB-positive -- were prepared for transfusions and for operation of the heart-lung machine used during the operations. Only four in every hundred persons have AB-positive blood. But, despite seriously depleted blood supplies due to the winter holidays, the NIH Blood Bank and the Washington Regional Blood Program of the American Red Cross quickly collected blood for both operations. Blood for open heart surgery must be collected a short time before the operations, in this case,

(more)

within five days of surgery.

The two organizations maintain rare donor files and work together to provide special blood needs. The American Red Cross supplies approximately 50 percent of the blood used at NIH for open-heart surgery. However, for the twins, the American Red Cross provided 21 units, while the Blood Bank collected seven.

Fortunately, the twins' surgery was completely "routine and unexciting," according to Dr. Andrew G. Morrow, chief of the Surgery Branch, National Heart, Lung, and Blood Institute (NHLBI), "and the girls should now show a very gratifying growth spurt." Because there were no difficulties, not all of the blood was used. Approximately ten pints were used to prime the heart-lung machine for both operations. The remaining blood will not be wasted, however, it can be used for other patients with this blood type up to three weeks after being drawn. After that, blood cells can be extracted and the liquid part of the blood, plasma, can be used.

The D'Alessio twins were admitted to NIH as part of NHLBI's research program on congenital heart disease. Only patients with a specific disease or condition under investigation by NIH physicians are eligible for admission at the Clinical Center and they must be referred by their doctors.

Only 16 hours after the twins had their hearts repaired by insertion of 2 x 3 centimeter Teflon patches over the defects, they walked from the intensive care unit to their rooms. Nine days later, they returned to their home in Newark, New Jersey, attesting to the surgical and nursing skill of the NIH team and the importance of that critical element -- blood -- available when needed.

(more)

OPEN-HEART SURGERY (CONT'D)

Cathy (left) and Jane (right), are happily at play in the 6th floor solarium, a few days after their open heart operations. (NIH Photo #1582)

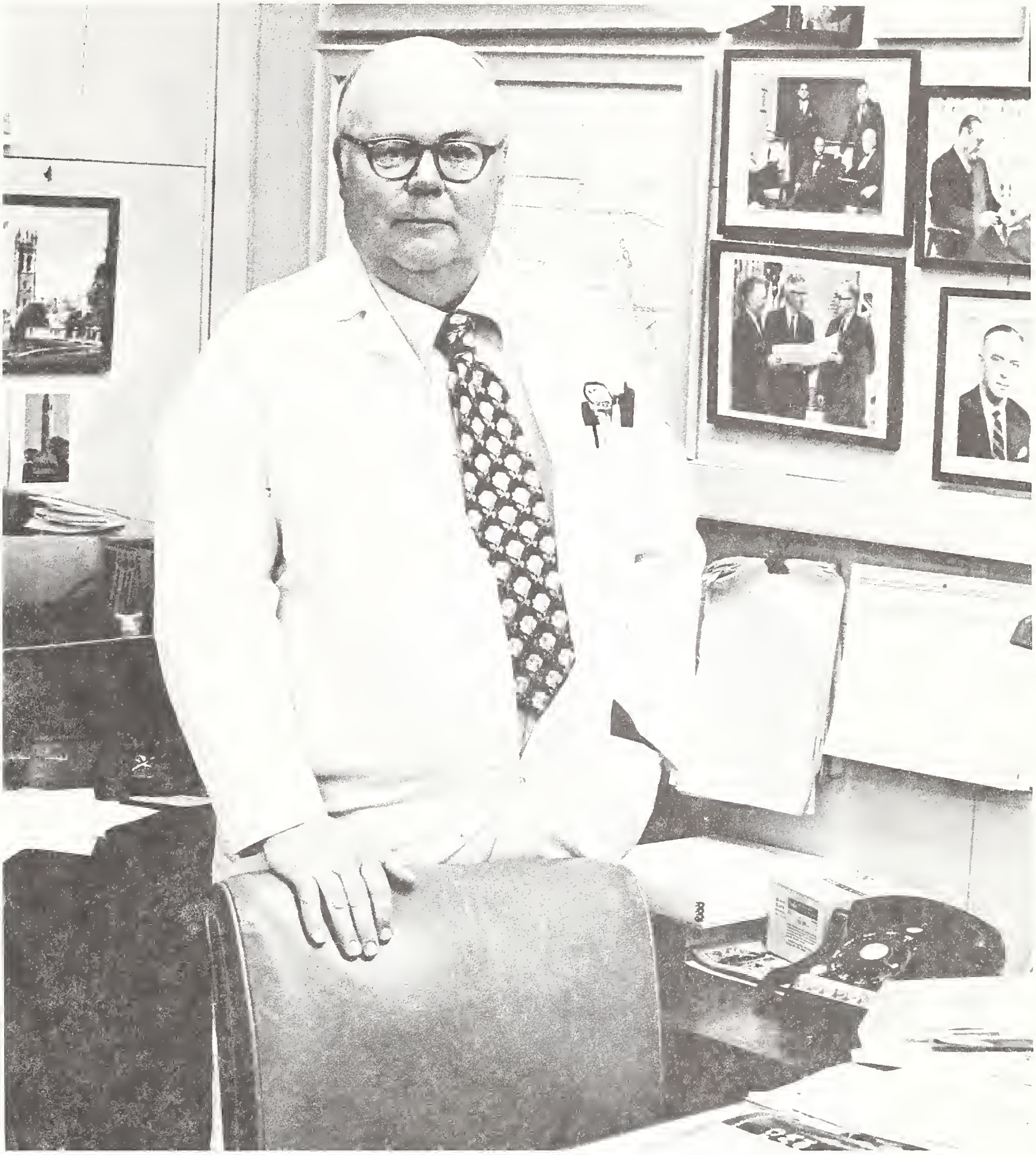
(more)

OPEN-HEART SURGERY (CONT'D)

Cathy (left) and Jane D'Alessio (right), shown here with their sister, Patricia, were born with atrial septal defects. Nine days after Dr. Morrow performed the operations, the 11-year-olds returned home in bright spirits. The twins are from a family of nine children and they live in Newark, N.J. Their widowed father, Pasquale D'Alessio, and Patricia (also a twin), were with them during their hospital stay. (NIH Photo #1583)

(more)

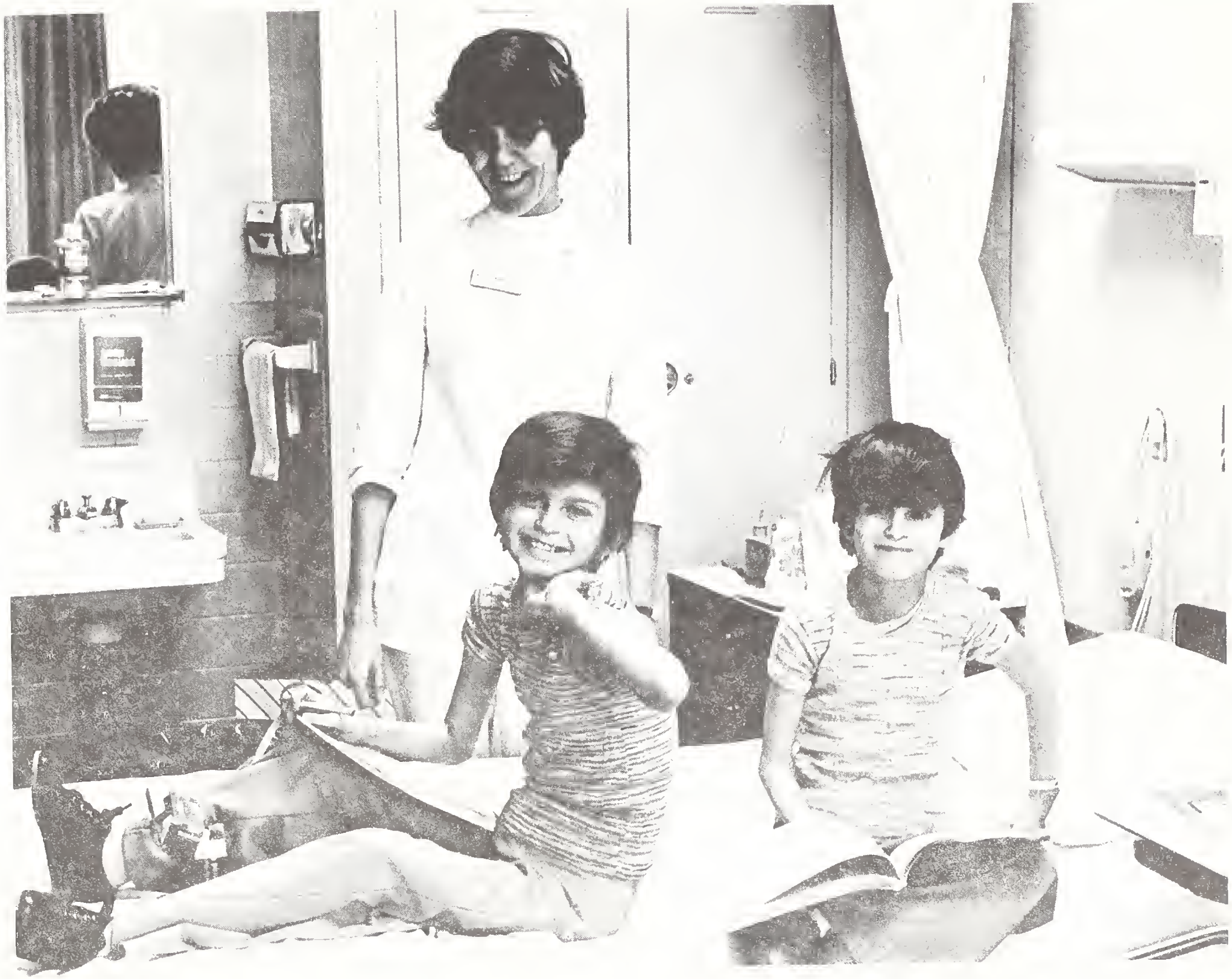
OPEN-HEART SURGERY (CONT'D)



Dr. Andrew G. Morrow, chief of the surgery branch, National Heart, Lung, and Blood Institute, operated on Jane, first born of the twins, at about 8:30 a.m., on January 27. At about 11, he began the same operation on Cathy with another team, completing it about 2 p.m. (NIH Photo #1584)

(more)

OPEN-HEART SURGERY (CONT'D)



Eleanor Bayer, the twins' primary nurse, was responsible for their care from the time they came on the unit to the day of discharge. Shown here with Jane (left) and Cathy (right), she planned and gave them their nursing care, and directed every facet of their discharge, to make their transition after surgery as smooth as possible. (NIH Photo #1585)

(more)

OPEN-HEART SURGERY (CONT'D)

Eleanor Bayer, the girls' primary nurse, helps them with some sessions on the "respirex". This is a form of deep breathing exercise to help increase pulmonary function after surgery. (NIH Photo #1586)

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Photo Feature

PEPTIDE HORMONES ARE POSSIBLE BRAIN REGULATORS

Although the control of the pituitary gland by a region of the brain known as the hypothalamus has been well established, the notion that various peptide hormones, may, in turn, control the brain is now being advanced.

Indeed, current investigations indicate that the brain itself may be an endocrine organ; that is, it may synthesize and release peptide hormones in order to influence brain activity.

The recent discoveries of endogenous opiate peptides in the pituitary and brain, and their profound behavioral effects, has intensified research into neuropeptides.

The well-known posterior pituitary hormones, oxytocin and vasopressin, are produced by specific nerve cells in the hypothalamus and are subsequently transported to the terminals of those neurons which are found in the posterior pituitary.

From these neuron terminals the hormones are released together with specific proteins known as neurophysins.

Although considerable indirect evidence in support of the hypothesis that these peptide hormones are derived from prohormones synthesized in the brain (similar to the relationship between insulin and proinsulin in the pancreas) has existed from some time, attempts to directly identify and isolate these prohormones have been unsuccessful.

In recent experiments, Dr. Harold Gainer of the National Institute of Child Health and Human Development and his colleagues, in collaboration with Dr. Michael J. Brownstein, National Institute of Mental Health, employed a novel combined microanatomic-biochemical approach to investigate this problem.

(more)

PEPTIDE HORMONES (CONT'D)

Using this approach, they discovered the prohormones for oxytocin, vasopressin, and neurophysin in the laboratory rat, and identified them by immunological techniques.

They demonstrated that while the synthesis of the prohormones occurs in the nerve cells in the brain, the transformation of these prohormones to the peptide hormones occurs in the nerve axons during transport to the pituitary.

Of perhaps greater significance is their finding that several previously undiscovered peptides, in addition to oxytocin and vasopressin, are synthesized in the brain and released by the posterior pituitary.

The functions of these newly discovered peptides are unknown at present, and whether they may represent new peptide hormones elaborated by the pituitary is now under investigation.

These experiments, in addition to showing that brain peptides are synthesized in a manner similar to peptide hormones in the endocrine system, also provide an experimental paradigm for the discovery of new peptides in the brain.

If, as has been proposed, brain function is under the control of neuropeptides, then identification and localization of these peptides in the brain will possibly provide new insights for the study of neurological and mental diseases.

(more)

Dr. Harold Gainer and his colleagues have found that several previously undiscovered peptides, in addition to oxytocin and vasopressin, are synthesized in the brain and released by the posterior pituitary. (NIH Photo #1587)

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NEWS & FEATURES From NIH

March 1977

News Feature

LATEX AGGLUTINATION TEST DIAGNOSES BACTERIAL MENINGITIS

Five new methods for rapid, accurate diagnosis of bacterial meningitis--including a latex agglutination test of cerebrospinal fluid that takes three minutes to administer and does not require sophisticated laboratory equipment--have been reported by Dr. Sydney Ross of the Research Foundation of the Children's Hospital National Medical Center, Washington, D.C.

The tests use either latex agglutination, lactic dehydrogenase, limulus lysate, lactic acid gas chromatography, or counterimmuno-electrophoresis.

The first three methods can be performed at the patient's bedside. None of the methods takes more than an hour.

The latex agglutination test "has the virtue of simplicity and rapidity," said Dr. Ross, "and can be adapted at hospitals without sophisticated labs."

Dr. Ross, a grantee of the National Institute of Neurological and Communicative Disorders and Stroke, described the methods at a recent pediatric symposium sponsored by Children's Hospital and the George Washington University Medical Center.

Previous methods for diagnosing bacterial meningitis tested spinal fluid for cell count, gram stain, and growth of disease organisms in culture.

The culture took one to two days--a delay in diagnosis which often led to unnecessary hospitalization and antibiotic treatment.

"The latex agglutination test is potentially the best," said Dr. Ross, "if cross-reactions can be eliminated."

The test does not always differentiate between the types of bacterial meningitis caused by *Hemophilus influenzae* and *Pneumococcus*.

Latex agglutination was 90 percent accurate in identifying 12 patients

(more)

MENINGITIS (CONT'D)

with *H. influenzae* meningitis (including five who had received prior antibiotic therapy), while negative results were obtained for nine patients with aseptic meningitis, two with herpes simplex, and 18 non-meningitis patients.

The other four methods varied from 93 to 100 percent accuracy. Lactic acid gas chromatography was 100 percent accurate, as was lactic dehydrogenase for patients who had not been previously treated with antibiotics.

Limulus lysate was 98 percent accurate, and counterimmuno-electrophoresis accurately diagnosed 93 percent of the patients who had not received previous antibiotic therapy.

Dr. Ross' associates were Dr. William Rodriguez, Dr. Waheed Khan, Dr. Alan Coit, Dr. Robin Goldenberg, and Guido Controni.

#

NEWS & FEATURES From NIH March 1977

News Feature

NEW NIGMS PROGRAM WILL HELP MINORITY STUDENTS

A new program of awards to help minority schools train undergraduate honor students for careers in biomedical research and teaching has been announced by NIH's National Institute of General Medical Sciences.

According to Dr. Ruth Kirschstein, Institute Director, the awards are intended to increase the number of minority students who can compete successfully for entry into graduate programs leading to the Ph.D. degree in biomedical science fields.

Grants will be made to qualifying institutions to develop a strong science curriculum, enhance laboratory and faculty capabilities, and assist students with tuition and stipend support.

Eligible institutions include those four-year colleges and universities within the United States and its territories whose student enrollments are drawn substantially from ethnic minority groups, namely American Indians, Blacks, Hawaiians, Mexican Americans and Puerto Ricans. It is expected that about $1 million will be allocated for this effort over the next year. Each grant will have a commitment of continuing support, up to a maximum of five years.

The selection of students for training will be a prerogative of the grantee school. On average, each grant will encompass training for five to ten students. Trainees as a rule will be chosen from among honor students in either their third or fourth years of college.

The honors undergraduate award program is an extension of biomedical science training support administered by the sponsoring Institute's Minority Access to Research Careers (MARC) program. Other forms of support offered

by the MARC program are Faculty Fellowship Awards, which further the training of minority institution bioscience faculties, and Visiting Scientist Awards, which help minority schools bring outstanding scholars to their campuses to strengthen health science research and teaching.

The Institute has the major responsibility at the NIH for the support of predoctoral research training with the objective of ensuring that the Nation's long-term need for well-trained biomedical research scientists is met.

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NEWS & FEATURES From NIH

March 1977

News Feature

NEW LEGISLATION IS "NECESSARY" IN USE OF RECOMBINANT DNA MOLECULES

New legislation is necessary to regulate the use and production of recombinant DNA molecules, according to a report transmitted on March 16 to the Secretary of Health, Education, and Welfare.

In accepting the report from the Federal Interagency Committee on Recombinant DNA Research, Secretary Joseph A. Califano, Jr., said that the Department will immediately begin drafting legislation in the light of the recommendations made by the Committee.

Califano noted that he had been closely monitoring the recombinant DNA issue since his confirmation and that he had been in continuous communication with Donald S. Fredrickson, M.D., NIH Director and the Chairman of the Interagency Committee.

"I recognize that legislation in this area would represent an unusual regulation of activities affecting basic science but the potential hazards posed by recombinant DNA techniques warrant such a step at this time," Califano said.

"But I believe that such a measure is necessary not just to safeguard the public but also to assure the continuation of basic research in this vital scientific area.

"We are not saying that research should be halted. We are urging that it should proceed under careful safeguards unless and until we have a better understanding of the risks and benefits posed by use of recombinant DNA techniques without government regulation," Califano said.

While agreeing with what he called the prudent recommendations of the Interagency Committee in this limited and most exceptional area, Califano

reaffirmed his commitment to the principle of unfettered inquiry that applies in scientific research.

The Interagency Committee is composed of representative of Federal departments and agencies that support and conduct recombinant DNA research or that have present or potential regulatory authority in this area.

The Interagency Committee recommended that any legislation should, among other things:

- place primary responsibility for the administration of the act on the Secretary of HEW;
- require any person engaging in such research, production, or use of DNA recombinant molecules to do so only at a facility licensed by the Secretary;
- require any person engaging in such activity to do so only after the project has been registered with the Secretary; and
- the Secretary should have authority to inspect facilities, make environmental measurement, and take other steps to ensure safety.

The Committee pointed out that this legislation would establish uniform standards for such activities throughout the Nation.

In addition, the Committee recommended that the NIH Guidelines for Research Involving Recombinant DNA Molecules become the national standard, with such modifications as the Secretary may consider necessary.

Califano stated that he asked HEW's General Counsel-Designate to work with Dr. Fredrickson and the technical experts on the Interagency Committee, and to consult closely with the relevant Congressional committees in drafting

legislation for clearance with the Office of Management and Budget and eventual submission to Congress, that would follow the Interagency Committee's recommendations.

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CONGENITAL MALFORMATIONS--In the United States in a single year, as many as 200,000 children will be born with one or more congenital anomalies. These malformations probably result from an interaction between genetic and environmental causes, according to the National Institutes of Health.

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March 1977

NEWS & FEATURES From NIH

News Feature

CHANGES IN PROCESS ARE SEEN FOR PEER REVIEW

Changes in the National Institutes of Health (NIH) grants peer review process have been recommended by the agency's Grants Peer Review Study Team, according to NIH Director Donald S. Fredrickson.

Among the recommendations of the Study Team were:

* A formal NIH Grants Peer Review Appeals System should be established, including an ombudsman to be appointed by the NIH Director.

* Upcoming vacancies on Initial Review Groups should be announced periodically.

* The principal investigator should be sent a copy of the summary statement associated with his or her application as soon as possible after the grant application is reviewed by the National Advisory Council or Board.

Dr. Fredrickson will announce shortly his decisions regarding implementation or further study of each of the individual recommendations.

The NIH grants peer review system is a two-step process, involving initial review for scientific merit and second review for merit and policy by national advisory groups. There are 77 Initial Review Groups and 13 National Advisory Councils and Boards.

The NIH Grants Peer Review Study Team consists of scientists and administrators of the National Institutes of Health. The Study Team is headed by Dr. Ruth L. Kirschstein, Director of the National Institute of General Medical Sciences.

The report, which is Phase I of a two-phase study, is based, in part, on testimony presented at three public hearing (held in Chicago, San Francisco,

(more)

and Washington, D.C.), letters from scientists and the general public, and the results of a survey of NIH advisors.

Phase II, to be completed in late 1977, will contain a detailed analysis and evaluation of the public testimony and the survey of Initial Review Groups and Council members.

Other major recommendations of the Study Team were:

* The NIH Director should be delegated the authority to establish or discontinue Initial Review Groups.
* The Assistant Secretary for Health, HEW, should be delegated the authority for selection and appointment of members of Advisory Councils.
* Portions of the meetings of advisory groups which involve the review of grant applications should continue to be closed to the public (including those submitting applications).
* The workload of the Initial Review Groups should be limited to help ensure a high quality of review.

The Study Team also made recommendations concerning a variety of other key issues. These include identification and special consideration of unorthodox research approaches, conflict of interest procedures applicable to review group members, increased use of business management consultants as an adjunct to scientific review, and continuing studies of procedures designed to improve the grants peer review system.

Copies of the report are available on request.

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NEWS & FEATURES From NIH

March 1977

News Feature

NICHD TO HOLD PRESS BRIEFING IN SAN FRANCISCO ON APRIL 26

The National Institute of Child Health and Human Development, in conjunction with the Society for Pediatric Research (SPR) and the American Pediatric Society (APS), will hold a briefing for media representatives and free-lance writers on the afternoon of Tuesday, April 26, at the San Francisco Hilton.

Topics for the briefing include current issues in child health research such as high risk pregnancy, amniocentesis, immunization, and human genetics. Panelists are experts in pediatric research from the West Coast and other parts of the country.

All communicators interested in health research issues--media representatives, free-lance writers, and editors--are invited.

For additional information about the briefing, call R. Anne Ballard, Public Information Officer, National Institute of Child Health and Human Development, Bethesda, Maryland at (301) 496-5133.

The briefing is scheduled during the annual meetings of the Ambulatory Pediatric Association (April 25-26) and the APS and SPR (April 27-29). A press room, located in the Hilton, will be staffed during the meetings by the News Services Department of the University of California at San Francisco. Contact: Claire Wray (415) 666-2557, or (415) 648-4443.

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Research Advances

MODIFIED FAST DIET MAY HELP TO CONTROL OBESITY

Research supported by the NIH has found a promising dietetic approach to controlling obesity. The diet consists of a modified fast which permits a minimal daily intake of protein, thereby avoiding the debilitating effects of a total fast.

Total fasting reduces or eliminates hunger, and is effective in inducing rapid weight reduction. However, a considerable portion of the reduction in total fast is not fat but lean protein tissue. Up to half the weight loss is protein in the first month, and one-third to one-fourth thereafter. In addition, total fasting has undesirable effects on the function of the liver and the kidney. Previous research has indicated that limited amounts of protein may prevent these side-effects.

Investigators supported by NIH's National Institute of General Medical Sciences and the Division of Research Resources have found that the daily consumption of 1.2 to 1.5 grams of protein per kilogram of the patient's ideal lean body weight preserves lean tissue and prevents liver or kidney dysfunction. Lean hamburger is approximately one-third protein, which translates roughly into 4 oz. of hamburger for every 50 pounds of ideal body weight. Given as lean beef or egg white, this small amount of protein does not interfere with the reduction or elimination of hunger.

The protein-sparing modified fast also includes an over-the-counter multivitamin, a potassium supplement, four antacid tablets containing calcium carbonate, water, and table salt.

This regimen was instituted for four young adults with Prader-Willi

(more)

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OBESITY (CONT'D)

syndrome, a genetic disease characterized by mental retardation, short stature, muscular laxity, and obesity. Obesity in this syndrome is thought to occur because of a non-functioning satiety center, which is located in the hypothalamus and regulates appetite. Gross overweight leads, in turn, to diabetes and respiratory impairments which are responsible for much of the early mortality in Prader-Willi syndrome.

The four patients were admitted to the Massachusetts Institute of Technology Clinical Research Center and received a thorough physical examination and clinical workup. Each week during their initial two-month stay a complete blood count and urinalysis was performed. The two male patients had clinical diabetes.

All the patients adhered to the regimen as inpatients, but had varying success as outpatients. One male patient went from 257 pounds to 123 pounds in 12 months, and has since stabilized at 134 lbs. A 250-pound female patient dropped to 174 pounds in 28 months but has crept back up to 189 pounds since then. The other male patient, a 12-year-old, lost 26 pounds in eight months but then began departing from the diet and weighed 55 pounds more than his admission weight before completely leaving the study.

When the desired weight loss was achieved in the successful male patient, a maintenance diet was instituted consisting of the same amount of protein, several glasses of skim milk, vegetables as desired, table salt and the multivitamin tablet.

The two female patients maintain the fiction of observing the modified fast, but their gradual regain strongly suggests incomplete adherence.

The two male patients had a rapid improvement in their diabetes and all

(more)

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OBESITY (CONT'D)

the patients had lower blood pressure and pulse rate. There were no important biochemical changes noted in the patients during the initial period, and lean body tissue was spared in the weight loss.

The investigators feel that the protein sparing modified fast offers a very useful experimental approach towards controlling obesity in the Prader-Willi syndrome, and may be of use in the larger problem of childhood obesity. They caution, however, that these findings are preliminary and a long-term followup is necessary to properly define the role of their dietetic approach to obesity in general.

This research was reported in the April 7, 1977 issue of *The New England Journal of Medicine*. The investigators were Dr. Bruce R. Bistrain of the New England Deaconess Hospital, Boston, Dr. George L. Blackburn of the Massachusetts Institute of Technology Department of Nutrition and Food Science, Cambridge, and Dr. John Stanbury of the Harvard Medical School, Boston.

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April 1977

NEWS & FEATURES From NIH

Research Advances

MONKEYS ARE USED IN STUDY OF MYOPIA

A simple and effective technique for inducing myopia in monkeys has been devised by NIH-supported researchers at the Harvard Medical School. This research, funded by the National Eye Institute, will aid in the study of nearsightedness, a condition which afflicts a significant percentage of the more than 94 million Americans who need corrective lenses.

The etiology of myopia has been studied primarily by investigating the distribution of refractive errors in human populations. No clear understanding emerged, and the prevailing clinical attitude is that nearsightedness can neither be prevented nor cured, but corrected with appropriate lenses. The causative factors in myopia can be rationally analyzed only if a suitable animal model is found. Previous studies of monocular sight deprivation in monkeys noted that an eye which had been closed by suture at birth developed a high degree of myopia.

The investigators in this study, Drs. Torsten N. Wiesel and Elio Raviola, sutured one or both eyelids of ten rhesus monkeys at various times after birth. The lid fusion was performed under general anesthesia sometime between birth and maturity.

The stitches were removed one to two weeks later and the lids were left fused for as little as 19 days and for as many as 26 months.

Upon reopening, the eyes were examined and measured using various non-invasive techniques such as the retinoscope and hand-held trial case lenses.

At various times after lid opening the monkeys were killed and the eyes removed for measurement and microscopic investigation.

A striking example of the results obtained is represented by a monkey

(more)

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MYOPIA (CONT'D)

whose right eye was closed at two weeks after birth and kept fused for 18 months. When opened, the eye had a normal appearance and surface development, nearly identical to the left eye, which served as a control.

The difference in the curvature of the anterior cornea between the two eyes was slight, but retinoscopy showed that the right eye was 13.5 diopters more myopic than the left.

At autopsy, the right eye was found to be considerably larger, over 4 mm or 21 percent longer in axial length than the left. Neonatal lid fusion had caused an elongation of the eye globe, distending the rear hemisphere and thinning the posterior sclera. All of the remaining ocular structures seemed unchanged.

The myopia resulting from lid fusion was clearly of the axial type; the corneal refraction was not altered significantly. Larger refractive errors were obtained in younger animals; the single mature monkey which underwent lid fusion showed no alteration in ocular size or focus. A separate experiment also demonstrated that the development of myopia in each eye is independent of the functional state of the other eye.

The fact that the refractive error is greater when lid fusion is performed early in life leads the investigators to believe that this form of myopia represents a derangement in the development of the eye. The elongation of the rear half of the eye parallels the previous observation in humans that the cornea is little changed after birth, but the axial length increases dramatically.

Neonatal lid fusion for the study of myopia appears to be a simple and effective research technique. According to the investigators, the fact that

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(more)

the other eye can be used as a control makes lid fusion a very useful animal model for myopia, and a study of its pathogenesis may provide insights into development of nearsightedness in humans.

This research was reported in the March 3, 1977 issue of *Nature*.

#

DENTAL IMPLANTS--Implants are non-living materials placed in the body to substitute for damaged or missing parts. For the past 20 years, some researchers have investigated surgical metals, plastic covered metals, acrylic plastics, and ceramics as dental implants. However, the National Institutes of Health does not recommend any type of tooth implant for public use.

DENTAL REPLANTS--Replants are teeth that have been knocked out by accident and then are replaced in the same socket. According to the National Institutes of Health, the replant procedure is relatively simple, often painless, and works most effectively on a child's tooth which has been out of the mouth less than an hour.

DENTAL TRANSPLANTS--Dental transplants are natural tissues or organs which are inserted as a replacement for a missing tissue or organ, coming from the same person or from someone else. National Institutes of Health studies have shown that soaking the tooth in a fluoride solution may prolong the success of the transplanted tooth.

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Research Advances

DATA FOUND ON HOW BIRDS CAN COPE WITH FLIGHT

An analysis made by New Mexico State University biomedical researchers of the breathing complexity of domestic pigeons at high temperatures may explain the mystery of how birds cope with the physical ordeal of flight. Their studies, although base line, could eventually enable scientists to gain new insights relevant to human problems of oxygen starvation.

The researchers have advanced the explanation that compound ventilation during heavy breathing makes it possible for birds to experience heat stress, such as that associated with flight, without disrupting the delicate acidity balance of the blood.

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Dr. Marvin Bernstein, associate professor of biology, and a team of undergraduate scientists have been monitoring breathing patterns and blood chemistry of domestic pigeons by use of thermal control boxes and hot-wire platinum sensors in their laboratory at Las Cruces, New Mexico, in the effort to develop a possible mechanism for minimizing hypocapnic alkalosis (deficiency of carbon dioxide in the blood).

The research is one of several conducted at the university under the Minority Biomedical Support program activity sponsored by NIH's Division of Research Resources.

Because birds do overheat in flight, as a human might running, they pant to cool off. This process is called evaporative cooling. During such panting or hyperventilation, a mammal would lose an excessive amount of carbon dioxide causing a drastic drop in blood acidity and eventual death.

While monitoring a pigeon's respiration, the researchers found that during rest, the bird breathed like a mammal with deep, even inhaling and exhaling.

(more)

BIRDS (CONT'D)

Under mild heat stress, it appeared that the bird's breathing became shallow and rapid, as would a mammal's. But under closer testing, they found that the heat-stressed bird practiced both methods of breathing, one superimposed upon the other.

Enough air goes deep into the bird's lungs to carry on body processes, but most is confined to the mouth where the evaporative cooling takes place. The researchers then found that under extreme heat stress, both components (maxi and mini breaths) became deeper. Air to the lungs increased; carbon dioxide in the blood decreased, which should have reduced blood acidity to dangerous levels. But the blood acidity did not go down as expected.

Blood acidity is dependent on temperature as well as carbon dioxide. With rising temperature, acid in the blood increases.

The researchers now believe birds lose carbon dioxide by hyperventilating, which would decrease blood acidity; but this decrease is offset because the bird allows its body temperature to rise, which would increase acidity.

"Thus, caught between these equal and opposing factors, the bird's blood acidity remains steady at health levels," Dr. Bernstein reports.

To investigate the compound breathing response in minute detail a small micro-anemometer flowmeter, encased in a mouthpiece, was used. The lightly restrained pigeons wore the mouthpiece so that all respiratory air passed through the flowmeter with no increase in dead space or resistance to air flow.

After suitable signal conditioning, the flow information was integrated after each respiratory half-cycle. This measured the volume of air inspired and

(more)

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BIRDS (CONT'D)

expired with each breath, which was recorded continuously on an oscillograph.

Working with Dr. Bernstein are four undergraduate scientists. They are John Ramirez, Felipe Samaniego, Miguel Escobedo, and David Gonzales. An initial scientific report on compound breathing of pigeons was made in the December 1976 issue of *Federation Proceedings* which contained eight papers produced by undergraduate scientists throughout the country participating in the Minority Biomedical Support program.

A further report of findings on the study was made by Felipe Samaniego at the annual Xavier-MBS Biomedical Symposium on April 11-13, 1977.

The project also receives support from NIH's National Heart, Lung, and Blood Institute.

(more)

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BIRDS (CONT'D)

New Mexico State University scientists are studying the respiratory pattern of pigeons in an effort to fathom how the birds can perform strenuous physical exercise at high altitudes without oxygen loss. Biologists Miguel Escobedo (standing left) and Felipe Samaniego compare oscillograph readings as David Gonzales (seated) places lightly restrained pigeon in position for heat stress breathing examination. The work is supported by NIH's Division of Research Resources through its Minority Biomedical Support Program. (NIH Photo # 1588)

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April 1977

NEWS & FEATURES From NIH

Research Advances

BLOOD CELL DEFECTS MAY AFFECT SOME TOOTH-SUPPORTING BONE

Scientists at the State University of New York at Buffalo, School of Dentistry, report that defects in certain white blood cells (polymorphonuclear leucocytes, or neutrophils) may contribute to the rapid loss of tooth-supporting bone in patients with periodontosis.

Periodontosis is a disease of young adults in which bone around the roots of a few specific teeth is lost rapidly.

This research, partially supported by NIH's National Institute of Dental Research, may explain why certain individuals have increased susceptibility to periodontal destruction.

The investigators found that neutrophils from nine young persons aged 16-31 years with periodontosis were less efficient both in migrating towards bacterial substances (chemotaxis) and in engulfing bacteria (phagocytosis), than cells from normal controls without periodontal disease. Other white cells (monocytes) from the same patients responded normally. A battery of laboratory tests and medical histories showed that the affected patients had no other medical problems.

The scientists also showed that neutrophils from a group of age matched patients with periodontitis, a chronic disease which differs from periodontosis, were normal with respect to both chemotaxis and phagocytosis. These results suggest that assessment of neutrophil chemotaxis and phagocytosis may distinguish the two diseases in individuals where clinical diagnosis is uncertain.

These findings suggest that either the causative bacteria are releasing a substance which depresses the neutrophils or that periodontosis patients have an intrinsic defect in their defense system. Preliminary evidence obtained

(more)

DEFECTS (CONT'D)

by the Buffalo team from families with two or more affected members indicated that the neutrophil defect is an intrinsic characteristic. In these families nondiseased siblings also showed the defect.

This research by Louis J. Cianciola, D.D.S., Robert J. Genco, D.D.S., Ph.D., Mark R. Patters, D.D.S., John D. McKenna, D.D.S., Carel J. van Oss, Ph.D., was reported in *Nature*, February 3, 1977.

#

SICKLE CELL--Sickle cell trait, the generally harmless condition, occurs about once in every ten American blacks. Sickle cell anemia occurs about once in every 500 American blacks. At present, it is estimated that there are about 50,000 persons in the United States with sickle cell anemia and about two million with sickle cell trait, according to the National Institutes of Health.

HEMOGLOBIN--The term "sickle cell disease" refers to all inherited blood conditions in which sickle cell hemoglobin is present. Hemoglobin is the red colored substance in red cells that enables blood to carry oxygen from the lungs to all tissues of the body, according to the National Institutes of Health.

Research Advances

ORAL SURGEONS STUDY BLOOD FLOW TO TISSUES

The use of surgery to correct facial deformities has increased rapidly in recent years. The clinical success of such surgery depends to a large extent on the preservation of an adequate blood supply to the tissues being altered especially the bony structures. The variations in rates of healing after surgery and the desire for optimal conditions prompted oral surgeons at the University of Minnesota to investigate the variability in blood flow to the tissues during different surgical techniques.

The research team, in work supported by NIH's National Institute of Dental Research, operated on 10 monkeys under controlled surgical conditions. They monitored blood pressure, heart rate, levels of carbon dioxide, and volume of red blood cells before, during, and after the operations.

The oral surgeons followed the same surgical techniques employed to correct protruding or receding upper jaws in humans. They measured the blood supply to various tissues when the palatine vessels were left intact and when they were severed. The scientists learned that the blood supply to the head region above the incision and to palatal tissue usually increased after surgery when those vessels were kept intact. Only the flow of blood to tooth-supporting bone and attached tissue decreased. If these palatine vessels were cut, the blood supply to the whole upper jaw and even to the lower jaw decreased markedly.

Just before surgery, tiny, radioactive carbonized spheres having a mean diameter of 15 microns, were injected into the heart to enable the scientists to measure blood flow to various tissues. About an hour after the operation, other microspheres, 15 microns and eight microns, labeled with different radioactive isotopes were injected simultaneously to allow measurements of

(more)

changes in the blood flow and in the diameter of small vessels. At the end of the experiment, samples of tissue from the mouth and various organs were also examined in a scintillation counter.

Animals with intact palatine vessels had comparable vascular measurements before and after the operation except for a 14 percent drop in the volume of red blood cells due to some loss of blood. However, the supply of blood above the cut tended to increase.

Although the animals with severed palatine vessels lost considerably more blood than the intact group, heart rates and blood pressures of the two groups were comparable.

However, the pattern of blood flow to various tissues differed in the intact and severed groups. In the intact group, the flow increased 10 percent to the palatal bone and 85 percent to the soft palate, but decreased 57 percent to alveolar bone and 37 percent to its attached gingiva. There was no change in blood flow to the lower jaw.

In the severed group, blood flow above the incision decreased slightly. The decrease to the palatal and alveolar bones was 89 percent, to the soft palate 47 percent, and to attached gingiva 95 percent. Moreover, blood flow to the lower jaw was also reduced.

The investigators believe that these findings should help to assure successful surgery and optimal healing conditions in the increasing numbers of patients undergoing facial surgery.

The study was reported in the *Journal of Oral Surgery*, January 1977, by Robert L. Nelson, D.D.S., Ph.D., Michael G. Path, D.D.S., Richard G. Ogle, D.D.S., Daniel E. Waite, D.D.S., and Maurice W. Meyer, D.D.S., Ph.D.

#

Photo Feature

ELECTRON PROBE PROVIDES NEW INSIGHTS INTO CELLS

A new area of research of the pituitary gland has recently been uncovered by use of electron probe microanalysis--an instrumentation which promises to have a wide-ranging effect on man's knowledge of the chemical makeup of living things.

The use of electron probe microanalysis at the Harvard Medical Center has determined that calcium is not uniformly distributed in the pituitary gland but concentrated in the intermediate lobe. As calcium is not present in high concentration in any living tissue except bones, the Harvard researchers report that they were surprised to find it in the intermediate lobe. This finding, made possible by use of the electron probe, may lead toward more complete comprehension of the physiology of the pituitary gland.

The electron probe microanalyzer is an extraordinary new instrument capable of localizing and quantitating any chemical element heavier than boron in sample volumes smaller than one cubic micron.

Funded in part by NIH's Division of Research Resources, Harvard's biotechnology resource in electron probe microanalysis, headed by Dr. Claude P. Lechene, is providing new insights into the study of structure and function of living cells.

The "probe" directs an electron beam at small freeze-dried samples, or scans a tissue preparation. Characteristic primary X-rays are emitted, depending on the chemical makeup of the sample. By determining the wave length and intensity of the emissions, researchers can ascertain the elemental chemical content of the sample.

An automatic stage moves the samples into position under the beam, spec-

(more)

trometers select the desired wave lengths, and the counters monitor those wave lengths.

A computer, through its multi-programming capability, simultaneously handles process-control functions (stage movement, beam control, spectrometer adjustment, and counter readings) as well as data analysis or on-line program development.

Complete analysis of human fluids, cells, and tissues is now possible, according to Dr. Lechene, a pioneer in electron probe microanalysis for biomedical research. The instrument can quantitatively measure any chemical elements, particularly the location and amounts of sodium, potassium, chlorine, phosphorus, calcium, magnesium, and sulfur-components of the major chemical compounds of the human body.

In reproduction research, for instance, the electron probe can make possible complete analysis of the fluids surrounding the ovum before discharge, during transit, and after implantation. The process can also analyze the internal composition of the early embryo.

In the area of renal function, the electron probe is capable of delving into all chemical transfers in the kidney; for example it can monitor sulfate levels in the kidney fluids.

The instrumentation is capable of doing individual chemical analysis of large populations of red blood cells which would allow investigators to observe composition changes as a function of age, sex, or disease state. This could be used in the study of leukemia, sickle cell anemia, diseases of the bone marrow, and other cell research areas.

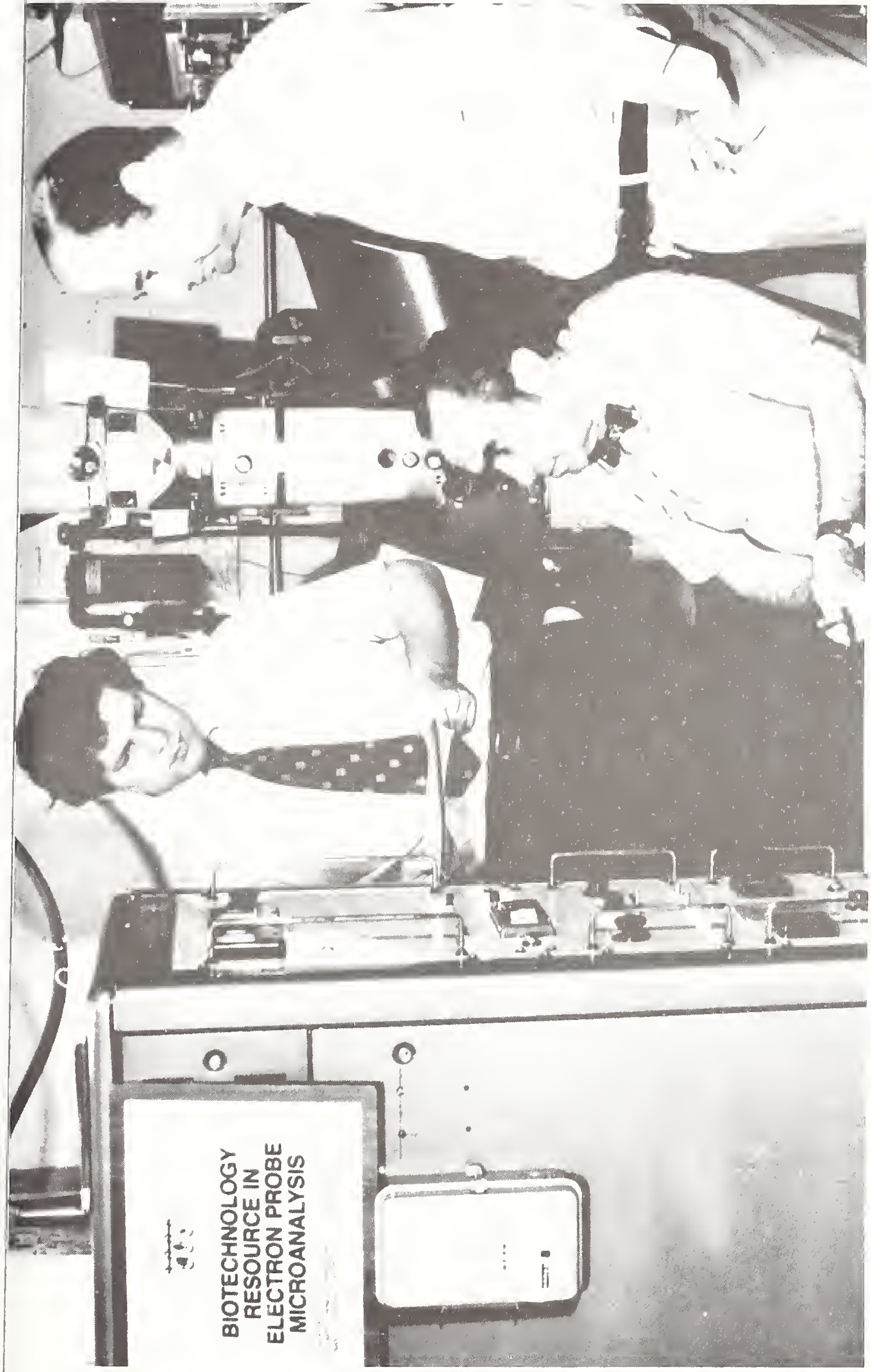
(more)

Additional NIH support to the resource is being made by the National Heart, Lung, and Blood Institute and the National Institute of Arthritis, Metabolism, and Digestive Diseases.

"The perfection of the electron probe will open up new studies of chemistry in cells," says Dr. Lechene. "It will probably give rise to discovery of new chemical labels in the field of cell biology. By labeling it should be possible to measure protein composition and localization in cells and tissues. We feel in the long run that electron probe microanalysis could have an important impact in biology comparable to, if not more important than, electron microscopy."

(more)

ELECTRON PROBE (CONT'D)



New insights on studies ranging from reproduction to hypertension are now possible with the use of the Harvard electron probe microanalysis facility which receives support from NIH's Division of Research Resources. (Left to right) Drs. Reinier Beeuwkes, A. Clifford Barger, and Claude Lechene are engaged in perfecting techniques for revealing chemical information never before known about microscopic structures. The electron probe was developed in the 1950's and used primarily in metallurgy. Constructed in 1973, the Harvard School of Medicine laboratory was the first electron probe resource in the United States for biomedical research. (NIH Photo #1589)

News Feature

NEW RABIES VACCINE IS FOUND EFFECTIVE

A team of U.S. and Iranian researchers, partially supported by NIH's National Institute of Allergy and Infectious Diseases, has successfully used a new rabies vaccine to treat 45 people bitten by rabid animals. Called a major medical advance, the vaccine is made from rabies virus grown in human cells; it has no side effects and protects with only six injections--making it the first completely effective weapon for protecting man against this generally fatal viral infection.

Once symptoms appear, there is no reliable treatment for rabies. Prompt, post-exposure vaccination can often prevent development of the disease, but not without potentially serious risks. Typically, administration of the current rabies vaccine -- grown in duck embryo cells -- requires anywhere from 14 to 21 injections -- with no guarantee of adequate immunological protection. In addition, some people experience allergic reactions to the foreign animal protein. These side effects range from painful swelling to paralysis and death.

The new vaccine, developed by Dr. Hilary Koprowski and his co-workers at the Wistar Institute of Anatomy and Biology in Philadelphia, is made from rabies virus cultured in W1-38 cells -- fetal human lung cells widely used in the production of other vaccines. Results from previous studies indicate that the new human diploid cell vaccine -- HDCV -- causes virtually no side effects and is highly immunogenic.

Convinced of the vaccine's safety and effectiveness, the investigators in the reported study set out to test HDCV in an area of the world where rabies is a serious problem. Physicians at the Pasteur Institute in Iran collaborated with the U.S. group in using the new vaccine -- coupled with antirabies serum --

(more)

RABIES VACCINE (CONT'D)

to treat a group of people severely bitten by rabid dogs and wolves between June 1975 and January 1976. As soon as the rabies-exposed victims could be reached, 44 of the 45 were given the antirabies serum for immediate protection. At that time -- four to 14 days after exposure -- they were also given their first injection of vaccine, followed by five more shots over a three month period.

Six to twelve months after treatment was initiated, the investigators reported that none of the victims developed rabies or experienced any adverse reactions to the vaccine. According to previous rabies statistics, about 35 percent would have died had they not been treated. What is even more striking, say the researchers, is the fact that treatment in some cases was started as late as 14 days after exposure. In the past, such delays have invariably resulted in failure to protect some of the exposed people from rabies death.

The scientists strongly recommend the use of antirabies serum with the vaccine for immediate, passive immunity during the critical post-exposure period. They suggest that the next step in improving rabies treatment is to produce immune-globulin from human cells to replace the antiserum of animal origin. This procedure is limited only by the availability of donors, such as the successfully treated persons in the present study.

Mahmoud Bahmanyar, Ahmad Fayaz, Shokrollah Hour-Salehi, Manouchehr Mohammadi and Hilary Koprowski from the Institut Pasteur de l' Iran, World Health Organization Collaborating Center for Reference and Research in Rabies, Tehran; and the Wistar Institute of Anatomy and Biology, World Health Organi-

(more)

zation Collaborating Center for Reference and Research in Rabies, Philadelphia, reported their research in the December 13, 1976 issue of the *Journal of the American Medical Association.*

#

SIDS--The sudden infant death syndrome (SIDS) is the leading cause of death in infants after the first month of life, claiming the lives of three infants for every thousand live births, according to the National Institutes of Health.

FOOD ALLERGIES--The most common food allergies are to fish, berries, nuts, eggs, cereals, milk, pork, chocolate, beans, and various fresh fruits. The National Institutes of Health reports that some people are also allergic to such substances as food additives.

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NEWS & FEATURES From NIH

April 1977

Photo Feature

NIH DIRECTOR SPEAKS TO 1,200 MINORITY SCIENTISTS

Dr. Donald Fredrickson, Director of the National Institutes of Health, was the keynote speaker at the Fifth Annual Minority Biomedical Support (MBS) Program-Xavier University Symposium in New Orleans April 11-13.

Approximately 1,200 biomedical researchers of minority origin--Black, Spanish-speaking, American Indian, and Hawaiian/Polynesian--attended the symposium, making it the largest minority biomedical research meeting. The symposium was co-sponsored by New Orleans' Xavier University of Louisiana and NIH's Division of Research Resources, through its Minority Biomedical Support Program.

The MBS Program, launched by DRR in 1972 with a $2 million budget, is intended to encourage increased involvement of ethnic minority students and faculty in the biomedical sciences and health professions. The funding allows grantee institutions to purchase necessary laboratory equipment, to free faculty scientists for research by hiring additional teachers, to conduct research programs, to pay the salaries of research personnel, and to participate in biomedical symposia, such as the New Orleans meeting.

There are now 80 colleges and universities participating in the program sharing a budget which has grown from the original $2 million to $9.7 million. Last year this budget supported approximately 1,800 researchers, including 970 undergraduates, 617 faculty and staff members, 176 graduate students, and 3 postdoctoral trainees.

This year's symposium had about 100 universities and colleges represented, with approximately 350 scientific research papers presented in biochemistry, microbiology, chemistry, physiology, pharmacology, parasitology, and other

(more)

SCIENTISTS (CONT'D)

biomedical research areas. Most of the papers were presented by student-researchers, but several speeches were made by world renowned scientists, such as Dr. Fredrickson.

The NIH Director told the researchers about the commitment of the National Institutes of Health to providing opportunities for minorities in biomedical research.

Another major address was given by Dr. Robert N. Butler, Director of NIH's National Institute on Aging. Dr. Butler detailed some of the special problems of aging among minorities and discussed access to careers in geriatric medicine for minority members.

The symposium was organized and administered by Dr. Joyce Corrington, director of Research in Science for Xavier University, and Dr. Ciriaco Gonzales, program director of the Minority Biomedical Support Program, Division of Research Resources.

(more)

SCIENTISTS (CONT'D)

A student chemistry researcher at Xavier University of Louisiana works on a research project which he reported on during the Fifth Annual Minority Biomedical Support Program-Xavier University Symposium in New Orleans. The symposium, the largest gathering of minority biomedical researchers, was funded by NIH's Division of Research Resources, under its Minority Biomedical Support Program. (NIH Photo #1590)

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April 1977

Photo Feature

OREGON OPENS NATIONAL CHROMOSOME REGISTRY

A national chromosome registry, the first of its kind in the nation, is in operation at the University of Oregon Health Sciences Center, Portland. The registry is funded by contract from NIH's National Institute of Child Health and Human Development.

Registry director Dr. Gerald Prescott, Health Science Center associate professor of medical genetics and perinatal medicine, said the registry will serve as a central collection point for information on aberrations (chromosome errors) which can cause birth defects, mental retardation, or both.

"Since aberrations are fairly rare, it's important to have a national collection point for information on them. Also, with all the breakthroughs in cytogenetics (the study of chromosomes) more aberrations are being discovered. This kind of effort to keep tabs on these findings is needed for improved patients care and medical research," he said.

The registry will catalogue and computerize the results of chromosome studies done on patients at the Health Sciences Center's Crippled Children's Division and five other regional registry centers across the nation. A chromosome is a microscopic body which carries genes that convey hereditary characteristics.

The other centers include the Yale University Medical School, New Haven; University of Tennessee Medical School, Memphis; University of Colorado Medical Center, Denver; Indiana University Medical School, Indianapolis; and Albany Medical College.

Computer work for the registry can help establish patterns of problems caused by aberrations. The registry will also be useful in genetic counseling

(more)

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REGISTRY (CONT'D)

with those couples who have a high risk of having children with chromosome problems.

There are about 6,000 patients now listed in the registry. By late 1977 about 15,000 are expected to be listed.

#

MONGOLISM--Maternal age is correlated with genetic defects in children. The chances of giving birth to a child with Down's syndrome are five to ten times higher for women over 35, according to the National Institutes of Health.

GOUT--Victims of gout can now be taken care of with reasonable comfort and can be assured that their disorder, if diagnosed early and treated properly, will not cripple them, according to the National Institutes of Health.

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SCIENTISTS SEEK TO INHIBIT BACTERIAL GROWTH ON TEETH

Boston scientists have extended for many days the time in which an antibacterial compound will adhere to teeth and inhibit bacterial growth.

For years microbiologists trying to combat tooth decay have been studying ways that bacteria use to cling to teeth long enough to colonize, multiply, and form sufficient acids to destroy enamel. Now investigators are studying ways to make antibacterial chemicals also stay on teeth despite the flushing action of saliva.

Drs. Joshua Greenberg, Samuel S. Turesky, and Victor D. Warner knew that 8-hydroxyquinoline (8-HQ) inhibits the growth of decay-causing bacterium, *Streptococcus mutans*, on teeth in the test tube. They also had evidence that suggested that this chemical attaches to teeth by combining with calcium and other metal ions on their surfaces and is gradually released. They reasoned that if they could improve 8-HQ attachment, an antibacterial environment could be maintained on the surface of teeth for long periods of time.

To measure the length of time that treated teeth remain antibacterial, the scientists developed an assay based on serial transfers of treated extracted teeth into fresh batches of sterile culture medium. After the teeth were removed, these batches were inoculated with *S. mutans* to determine whether the 8-HQ had leached from the teeth into the fluid, as indicated by antibacterial activity.

The investigators found that after the tooth had been immersed in the culture medium for 24 hours, there was no longer any evidence of antibacterial activity. However, if the tooth were treated with ferric or ferrous sulfate before applying 8-HQ, the antibacterial activity continued during more than six

(more)

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TEETH (CONT'D)

sequential 24-hour immersions in culture broth.

These encouraging laboratory findings cannot be directly translated into human use, but do suggest that there are ways to prevent saliva from flushing anti-bacterial chemicals from the mouth.

The research, supported by NIH's National Institute of Dental Research, was reported in the *Journal of Periodontology*, November 1976. Drs. Greenberg and Turesky are at the Tufts University School of Dental Medicine, and Dr. Warner is in the Department of Medicinal Chemistry and Pharmacology, Northeastern University, Boston.

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April 1977

NEWS & FEATURES From NIH

Research Advances

TASTE SENSATION CHANGES IN CANCER PATIENTS

Taste sensation changes when a patient has cancer, reports a Northwestern University cancer specialist, and may help account for the severe weight loss associated with the disease.

Since the loss of appetite is an important factor in the general debilitation, doctors have been concerned with ways to help patients increase food intake.

Working with 50 patients who have various types of cancer, Dr. William DeWys, associate professor and chief of medical oncology at Northwestern University Medical School, found that by heightening seasonings and watching individual food preferences closely he could help patients enjoy food again.

Dr. DeWys says that patients develop a higher threshold for sweet taste and a lower threshold for bitter taste as the disease progresses. The most common taste complaint is that the food is too bland, too "blah".

The taste abnormalities relate to the state of the cancer, he reports. Taste sensation was measured before and during therapy. As therapy reduced the tumor, the taste preferences normalized.

Dr. DeWys points out several implications of the altered taste sensation. Since taste triggers salivation, altered taste and inadequate salivation may account for the difficulty in swallowing reported bv patients. Abnormal taste may also lead to inadequate secretions and may explain the sense of early fullness. Good tastes stimulate pancreatic secretions. Inadequate pancreatic secretions may lead to sluggish digestion of the first meal of the day.

Further research is needed, he says, to clarify the physiological causes and to develop additional specific intervention strategies.

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TASTE (CONT'D)

Many patients in the study were able to eat more food when they added sugar or spices to it.

The substances in pork and beef, which most people like, were experienced as "bitter" by the patients who had developed a low threshold for bitterness. These patients were helped to cover the bitter taste with new tastes such as tomato, oriental sauces or strong seasonings. Alternatively, patients were able to substitute poultry, fish, eggs and mild cheeses for beef and pork.

The study was supported in part by NIH's National Cancer Institute and will be published as part of a series on Current Concepts in Nutrition.

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NEWS & FEATURES From NIH

April 1977

News Feature

DR. MAXINE SINGER, NCI, WILL GIVE MIDER LECTURE

Dr. Maxine F. Singer, head of the Nucleic Acid Enzymology Section of NIH's National Cancer Institute, will deliver the G. Burroughs Mider Lecture at 8:15 p.m., May 18, in the Jack Masur Auditorium of the NIH Clinical Center.

Members of the scientific community and the press are invited to attend.

Dr. Singer's address, "Monkey Business: Sequences in the Monkey Genome and Their Interaction with Simian Virus 40 DNA," will deal with her studies on the nucleotide building blocks of DNA (deoxyribonucleic acid) in the genes of normal monkey kidney cells and cells infected with the monkey virus SV40.

The genes of monkey cells--and all other animal cells--contain certain DNA nucleotide sequences that are repeated many times. These repeated sequences can become part of the DNA of new SV40 virus particles produced in infected cells. Dr. Singer has used enzymes to prepare DNA fragments containing repeated sequences from DNA of uninfected cells and from SV40 of infected cells. A comparison of nucleotide sequences in the fragments has led to an understanding of the repeated sequences and of the nature of the interaction between the virus and its host. This interaction may be related to the fundamental process by which a cell becomes cancerous.

Dr. Singer received her Ph.D. degree from Yale University in 1957. Since then, she has done extensive research in genetics and biochemistry at the National Institutes of Health and as a visiting scientist at the Weizmann Institute of Science in Rehovot, Israel.

The G. Burroughs Mider Lectureship was established in 1968 by the scientific directors to honor Dr. Mider for his distinguished service to NIH. The Lectureship is awarded by the NIH Director, on the advice of the scientific directors, to a scientist who has contributed significantly to biomedical research at NIH.

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Photo Feature

NICHD RELEASES BOOKLET ON LOW BIRTH WEIGHT BABIES

One in every 13 babies born each year in the United States is born too soon, too small, or both. These tiny babies (less than 5-1/2 pounds) are low birth weight infants and account for 70 percent of all deaths in the first year of life. Low birth weight is a serious disadvantage, and these babies often have problems handling such vital life functions as breathing, metabolism, excretion, and control of body temperature.

A new pamphlet of the National Institute of Child Health and Human Development (NICHD), Little Babies: Born Too Soon--Born Too Small, describes the problems these babies face, what measures physicians take to save them, what is known about the causes of low birth weight and what research programs are being undertaken to prevent premature births and gain a fuller understanding of the problem. Several maternal factors are associated with low birth weight, although not all premature or growth retarded babies are born to women who have one or more of these characteristics. Mothers at risk often:

* are under 16 years of age
* have previously given birth to a low birth weight infant
* are undernourished
* are suffering from a chronic condition (diabetes and certain infections)
* smoke cigarettes
* are alcoholics or addicted to narcotics
* have not had regular prenatal care
* have certain genetic disorders

Single copies are available free on request to the NICHD Office of Research Reporting, Building 31, Room 2A-34, National Institutes of Health, Bethesda, Maryland 20014.

#

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May 1977

Research Advances

TOPICAL APPLICATIONS OF ZINC READILY PENETRATE THE SKIN

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Animal studies, supported by NIH's National Institute of Dental Research, indicate that topical applications of zinc penetrate the skin so readily that it may be possible to correct human deficiences of this mineral by utilizing this simple method.

Nutritionists at the University of California, Davis, note that although the diet usually supplies the body's requirements for zinc, blood levels of this element drop rapidly when patients are fed intravenously. It is known that too little zinc during pregnancy can cause congenital abnormalities in animals and may lead to taste and skin problems in man. Extra zinc is needed to manage digestive and skin symptoms in victims of the human genetic disease, acrodermatitis enteropathica. Zinc is also used to promote wound healing and as a household remedy to sooth chapped and sunburned areas.

Concern for the problems of patients who cannot be fed by mouth or stomach tube led Lucille S. Hurley, Ph.D., and Carl L. Keen, B.S., to test the amount of zinc that would enter the blood of pregnant rats via the skin. They found that 24 hours on a zinc-deficient diet sharply reduced the plasma levels of zinc in all the animals. The animals were then treated with a chemical agent to remove the hair from a 3 x 4 square cm area of the back. An 8-hour exposure of the hair-free area to zinc chloride in oil at a concentration of 7,500 parts per million raised the amount of zinc in the blood to the same level as found in the control animals which were on a normal diet. A 24-hour exposure to the same zinc preparation increased the levels of zinc significantly.

These findings, together with some of their observations of human serum

(more)

ZINC (CONT'D)

levels, suggest that further research may show that zinc readily penetrates intact human skin. The scientists hope that enough zinc can thus enter the body to allow clinicians to treat cases of zinc deficiency with topical applications when patients can neither eat nor be fed by stomach tube.

This research, supported by a NIDR training grant, was reported in the *American Journal of Clinical Nutrition*, April 1977.

#

SORE THROAT--Penicillin and certain other antibiotics are effective destroyers of the streptococcus germ. Used promptly according to the doctor's orders whenever a sore throat or tonsillitis strikes, they can usually prevent the first attack of rheumatic fever, according to the National Institutes of Health.

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Research Advances

LAB TESTS SOUGHT TO DETERMINE CANCER RISKS

Development of laboratory tests to determine whether a person is at high or low risk of a certain type of cancer is one of the research objectives of the National Cancer Institute's Virus-Cancer Program, according to a statement April 19, 1977, by Paul H. Levine, M.D., at an NIH Science Writers Seminar.

Reviewing some highlights of the clinical studies carried out by the Virus-Cancer Program, Dr. Levine reported that while such tests are being sought, and some are in the developmental stages, none is ready for general use for the major forms of cancer affecting Americans. Tests giving advance warning of some rare forms of cancer, such as nasopharyngeal cancer, however, are close to field testing. Early detection of nasopharyngeal cancer is of importance, he stated, since the disease is extremely difficult to diagnose and usually must be treated early for optimum results. The disease often responds to radiation therapy.

Nasopharyngeal cancer is of interest to U.S. scientists for several reasons, Dr. Levine said, even though the incidence in the U.S. is not high. The disease, common among men in Southeast Asia, apparently reflects a genetic susceptibility. Laboratory tests indicate that Epstein-Barr virus (EBV) and chemical carcinogens may also play a role in its causation.

Dr. Levine said that a combination of tests for nasopharyngeal cancer susceptibility is being evaluated under a National Cancer Institute research contract by investigators at the University of Singapore. One mark of risk to this cancer is the presence on a person's white blood cells of a protein called Singapore-2, one of the histocompatibility antigens. A second appears

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to be an elevated level of antibody to EBV.

Although the study has concentrated thus far on persons living in Singapore and Hong Kong, Dr. Levine said it could be appropriate to start similar testing in Chinatown areas of New York City, San Francisco, and other parts of the U.S. A registry of American cases of nasopharyngeal cancer is being planned in conjunction with the Armed Forces Institute of Pathology and the Mayo Clinic.

The observation that high levels of antibody against EBV may signal an increased susceptibility to cancer is not new, according to Dr. Levine. In studies with the NCI Epidemiology Branch and the Center for Disease Control in Atlanta, he and his colleagues found that apparently normal individuals in cancer families had higher levles of EBV antibody than several control groups. Current studies are focusing on whether these tests can be used to detect specific individuals who may be more likely to develop cancer.

More evidence for the possibility that EBV antibody levels may indicate a cancer risk came recently from investigators at the International Agency for Research on Cancer (IARC), Lyons, France, who reported high antibody levels in children at high risk of developing Burkitt's lymphoma, a cancer predominantly affecting children in areas of Africa and other regions where malaria is holoendemic. Burkitt's lymphoma is another form of cancer where Epstein-Barr virus appears to be one of the causative factors. In a seroepidemiological study of more than 30,000 normal children in Uganda, Guy deThé, M.D., Ph.D. of IARC and his colleagues found that the levels of antibody to EBV were higher in the eight children who subsequently developed Burkitt's lymphoma than in the control children.

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(more)

CANCER (CONT'D)

Although field trials such as those planned in Singapore will help to determine the value of these tests in clinical programs, basic research must continue to investigate why some people have such high antibody levels to EBV. EBV is ubiquitous, but its activity differs among individuals and populations. In the Western world, for instance, EBV is the major cause of infectious mononucleosis, and has also been shown to cause acute tonsillitis. While most people throughout the world have antibodies against EBV, it is the level of antibodies that appear to reflect susceptibility to cancer, particularly certain types. Dr. Levine also noted that antibody levels have been useful in determining whether a patient with cancer was free of disease or having a relapse. In one study by the Mayo Clinic and NCI, recently reported by Gary Pearson, Ph.D., antibody levels to EBV signalled disease activity in two patients with nasopharyngeal cancer before signs of relapse were clinically apparent.

The reasons for these antibody differences are not clear at present, and Dr. Levine noted that much work remains to be done. Studies on the role of genetics and other factors determining antibody levels are in progress by several of NCI's Virus-Cancer Program contract laboratories.

Dr. Levine described other clinical projects where fundamental research supported by the Virus-Cancer Program has been translated into clinical applications.

George Bekesi, Ph.D. and James Holland, M.D., at Mt. Sinai Hospital in New York City had found that mice with naturally occurring leukemia caused by a virus were more effectively treated if a type of immunotherapy was added to the treatment. Following chemotherapy to reduce the tumor burden, anti-tumor response was augmented by intradermal inoculation of neuraminidase-

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treated cells. In addition, control of the oncogenic virus (Gross leukemia virus) was attempted by the use of antiviral drugs. Significantly prolonged survival was achieved in the mice. The New York investigators, working under an NCI contract, are evaluating a similar approach in treating patients with acute myelocytic leukemia.

In reviewing the complexities of applying viral tests to the diagnosis and monitoring of cancer patients, Dr. Levine noted that many forms of cancer, such as breast cancer, leukemia, and lymphoma, may present themselves in various distinguishable subtypes that may have either similar or different coordinated etiologies. As a result, he said, even if a virus were incontrovertibly proven to be associated with some cases of human cancer, this might not necessarily lead to a totally successful preventive vaccine.

On the other hand, further knowledge of any association of viruses with human cancer will lead, he believes, to greatly enhanced means for early and improved diagnosis and more successful treatments. These factors thus have led to the increased emphasis on the application of virologic tools in clinical oncology.

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NEW KNOWLEDGE IS GAINED ABOUT IMMUNE RESPONSIVENESS

Using inbred strains of mice, investigators at NIH and elsewhere have identified unique products of a subunit of the H-2 chromosomal locus that appear to control immune responsiveness. The gene region, called the Ir region, was described in the early 1960s by Baruj Benacerraf, M.D., and Hugh O. McDevitt, M.D., and their colleagues at New York University School of Medicine and Harvard Medical School, respectively.

The Ir region is located on the animal's 17th chromosome, within the H-2 locus that is known to be the major histocompatibility locus of mice. (H-2 is analogous to the HL-A chromosomal region controlling histocompatibility in man.)

The Ir region of the chromosome is now known to control production of Ir-associated antigens (Ia antigens), which are glycoproteins found on the surface of certain white blood cells--B lymphocytes. These cells, when mature, produce antibodies (immunoglobulins) which are a critical part of the immune defense systems of men and other animals.

The research on Ia antigens was described April 19,1977, at an NIH Science Writers Seminar by David H. Sachs, M.D., of the National Cancer Institute's Immunology Branch. Dr. Sachs emphasized that relevant findings in detecting Ia antigens were made independently and almost simultaneously in his own laboratory, and at Stanford University and the University of Michigan.

Pinpointing and isolating the Ia antigens may help to explain the function of Ir genes in controlling immune responsiveness, Dr. Sachs said. This could be an early step toward understanding immune defenses against various disease-causing agents. It might also lead to improvements in the acceptance or

(more)

RESPONSIVENESS (CONT'D)

tolerance to transplanted body organs and tissues used therapeutically.

Dr. Sachs postulated that the Ir region of the H-2 locus might be its most influential, active region. He said, however, that the natural function(s) of all H-2 subunits (K, I, S, and D) has not yet been fully defined.

Dr. Sachs said that the Ia antigens of men and animals appear to be very similar in size and chemical composition, as determined by scientists at NIH and many other institutions. Evolutionarily speaking, they have been "conserved" during speciation, which may indicate a great functional significance. Their function is a subject of study in Dr. Sachs' laboratory and elsewhere. Laboratory mice, because they are inbred and because strains can be produced to differ genetically only in the Ir region, provide an excellent laboratory tool for this type of study, he said.

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Research Advances

CHICAGO SCIENTISTS HAVE PURIFIED ERYTHROPOIETIN

Using urine specimens, University of Chicago scientists have obtained a pure sample of erythropoietin, a hormone that stimulates production of red blood cells.

The sample of human erythropoietin, eight times more active than previously reported pure sheep erythropoietin samples, will make possible a detailed study of erythropoietin's chemical and biological properties, says Dr. Charles K.-H. Kung, a University of Chicago biochemist.

If the chemical structure of erythropoietin can be discovered, a means may be found to create synthetic erythropoietin to treat anemia, in which there is a reduced ability of the blood to carry oxygen to the tissues.

When there is a need for increased red blood cells to deliver oxygen to tissue, the body normally increases the amount of circulating erythropoietin.

The hormone then "instructs" the blood-forming tissue (mainly in the bone marrow) to increase the production of red blood cells.

Erythropoietin is formed principally in the kidneys of humans and other mammals. Some victims of kidney disease are unable to produce their own body erythropoietin and require careful management and occasional blood transfusions.

Availability of enough pure hormone or synthetic erythropoietin might facilitate the treatment of anemia in kidney patients. At present there is not enough of the pure hormone for any treatment purposes.

Knowledge of how erythropoietin acts to form red blood cells from progenitor cells would be useful in the study of biological differentiation.

With erythropoietin available, this process can now be studied in progenitor

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cell cultures in the laboratory. Knowledge of normal and abnormal differentiation is needed to understand how cancer, birth defects, and other diseases may occur.

Dr. Kung, senior scientist in the Franklin McLean Memorial Research Institute in The University of Chicago Division of the Biological Sciences and The Pritzker School of Medicine, spoke April 7, 1977, at the annual meeting of the Federation of American Societies for Experimental Biology in Chicago.

Co-authors of Dr. Kung's paper were Dr. Takaji Miyake of Kumamoto University Medical School, Kumamoto, Japan, and Dr. Eugene Goldwasser, professor in the department of biochemistry, the McLean Institute and the undergraduate College at The University of Chicago.

Much more pure hormone will be needed before the structure of erythropoietin is finally established, says Dr. Kung.

Urine from specific kinds of patients is at present the only practical source of erythropoietin.

The best source for research purposes is the urine of aplastic anemia patients in which substantial portions of the erythropoietin spill over into the urine and are excreted.

Dr. Miyake and his collaborators at Kumamoto University collected 2,550 liters (676 gallons) of urine from aplastic anemia victims and prepared a crude concentrate of erythropoietin.

Dr. Miyake brought the crude erythropoietin to the McLean Institute, where, in collaboration with Drs. Kung and Goldwasser, a pure sample was prepared over a period of 1 1/2 years.

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ERYTHROPOIETIN (CONT'D)

The total yield--about 8 mg. (0.0003 oz.)--represented about 20 percent of the initial amount of hormone in the crude concentrate.

The process of purification required the use of seven different methods in succession and resulted in a sample of human erythropoietin with a potency of about 70,000 units per mg. of protein.

Isolation of pure erythropoietin from the blood of anemic sheep was first reported by Drs. Goldwasser and Kung in 1971.

The existence of mammalian erythropoietin has been known for at least 70 years, according to Dr. Goldwasser, but it is present in such minute traces that until 1971 it was never isolated in pure form.

The assay procedures required to carry the work to this point were developed by Dr. Leon O. Jacobson, currently the director of the McLean Institute; and Drs. Goldwasser, Walter Fried, and Louis Plzak at The University of Chicago. These methods led to their finding in 1957 that the kidney is the major source of erythropoietin.

The McLean Institute is operated by The University of Chicago under a contract with the Energy Research and Development Administration.

The current research was supported by the ERDA grant to the McLean Institute and by a grant from the National Heart, Lung, and Blood Institute to The University of Chicago Comprehensive Sickle Cell Center, directed by Dr. James Bowman.

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Research Advances

STUDY SEEKS WAY TO DETECT CHANGES IN CENTRAL NERVOUS SYSTEM

Enzyme aggregates (called isozymes), previously identified with the brain, were detected in the serum of half of a group of over 90 patients with multiple sclerosis by combining information from three different analyses. The results of this study, designed to provide sensitive means of determining changes in the central nervous system, were reported at the April 1977 meeting of the Federation of American Societies for Experimental Biology in Chicago by Dr. Ann E. Kaplan, a biochemist at NIH's National Cancer Institute, and Drs. George W. Ellison and Lawrence W. Myers, co-directors of the clinic for multiple sclerosis at the Reed Neurological Research Center, University of California at Los Angeles.

This study was undertaken in an attempt to develop tests to inform the physician of the ongoing state of the patient since neurological symptoms often do not appear until some time after local changes take place in the brain. Furthermore, the methods enable the physician to evaluate the condition of the central nervous system as a whole, including those regions which do not control well-defined neurological activity and are considered to be the "silent areas of the brain" in neurological terms. It is hoped that the physician will be able to make practical use of the molecular changes detected by the methods reported in this paper as work in other areas of this disease progresses and therapeutic methods are developed.

The results are based on the measurements of the activity and molecular composition of the enzyme, lactate dehydrogenase (LDH), in serum. This enzyme is found normally in cells of the body as well as in serum. It exists in five known aggregates, called isozymes. Characteristically, different organs of the

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(more)

body have one or two types, but not all five isozymes. The appearance of specific patterns of isozymes of LDH in serum serves as a useful indicator of clinical disease in cardiac and liver damage.

This study, which suggests that serum LDH changes can also serve to indicate changes in the central nervous system, is based on results of a lengthy investigation with animals by Dr. Kaplan when she was on the staff of the Salk Institute in San Diego, California. The earlier study made use of immunological means to induce destruction of the brain tissue in rabbits. It was found that the isozymes appearing in the rabbit serum, LDH-2 and LDH-3, were identical to those extracted from the animal's brain, and that the time course of the appearance of these isozymes in serum corresponds to the period of damage to brain tissue observed upon histological examination.

In the study with patients with multiple sclerosis, three methods of analyses were used to confirm the leakage of LDH from the brain into the serum after samples were centrifuged at least twice to remove all cells. The first two methods applied were the determination of total activity and the separation of the isozymes by gel electrophoresis. These procedures are carried out in most clinical laboratories, although the latter method sometimes presents difficulties. The third method takes advantage of the fact that in measurements of reaction rates, the isozymes from brain are less inhibited under conditions which lead to the partial inhibition of the isozyme mixture found normally in serum.

Thus a serum sample enriched with isozymes from the brain will be proportionately less inhibited in measurements of the rate of enzyme reaction

(more)

SYSTEM (CONT'D)

than normal serum under the test conditions used. This method was developed originally for the evaluation of cardiac infarction in the laboratory of Dr. Nathan O. Kaplan (not related) at the University of California, San Diego. The instrumentation for this analysis was developed by the American Instrument Company, Silver Spring, Maryland.

This study is one of several collaborations Drs. Ellison and Myers are engaged in as part of their clinical research program. The clinic at UCLA is the first one devoted to multiple sclerosis in the United States. It was organized in 1958 by Dr. Augustus S. Rose, a pioneer in the concept of sustained services for the many needs of the patient and family with respect to this disease.

This investigation was supported in part by NIH's National Institute of Neurological and Communicative Disorders and Stroke.

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Photo Feature

NLM EXHIBIT IS BASED ON MEDICINE AND MUSIC

The belief in the power of music to drive out evil spirits or to summon beneficent ones has a long history. NIH's National Library of Medicine, drawing on its extensive historical resources, is making Medicine and Music the subject of an exhibit open to public viewing from May 2 to August 26.

Visitors will learn about tarantism, a disease believed in the 17th and 18th centuries to be caused by the bite of the tarantula spider and to be cured by music (the "tarantella") which induced the victim to participate in a frenzied (and curative) dance. The exhibit also features an audio recording excerpted from Marin Marais's *Tableau de l'Operation de la Taille.* This is a musical description of a lithotomy (an operation for the removal of stones), composed for viola da gamba and harpsichord and published in 1725. The composer, who had survived this operation a few years earlier, gives musical expression to the patient's feelings at each step of the surgical procedure. In addition, the exhibit includes a number of books, ranging from the 17th to 20th centuries, which show the development of theories attempting to explain the physiological effects of music.

Notes on the relationship between medicine and music through the ages will be found in a brochure ("Medicine and Music"). The booklet is available without charge at the exhibit, or by writing to the Library's Office of Inquiries.

The National Library of Medicine is at 8600 Rockville Pike, Bethesda, Md. The exhibit may be viewed weekdays from 8:30 a.m. to 9 p.m. and Saturdays from 8:30 a.m. to 5 p.m. Summer hours (8:30 a.m. to 5 p.m., Monday-Saturday) go into effect May 31st. The Library is closed on Sundays and on May 28, May 30,

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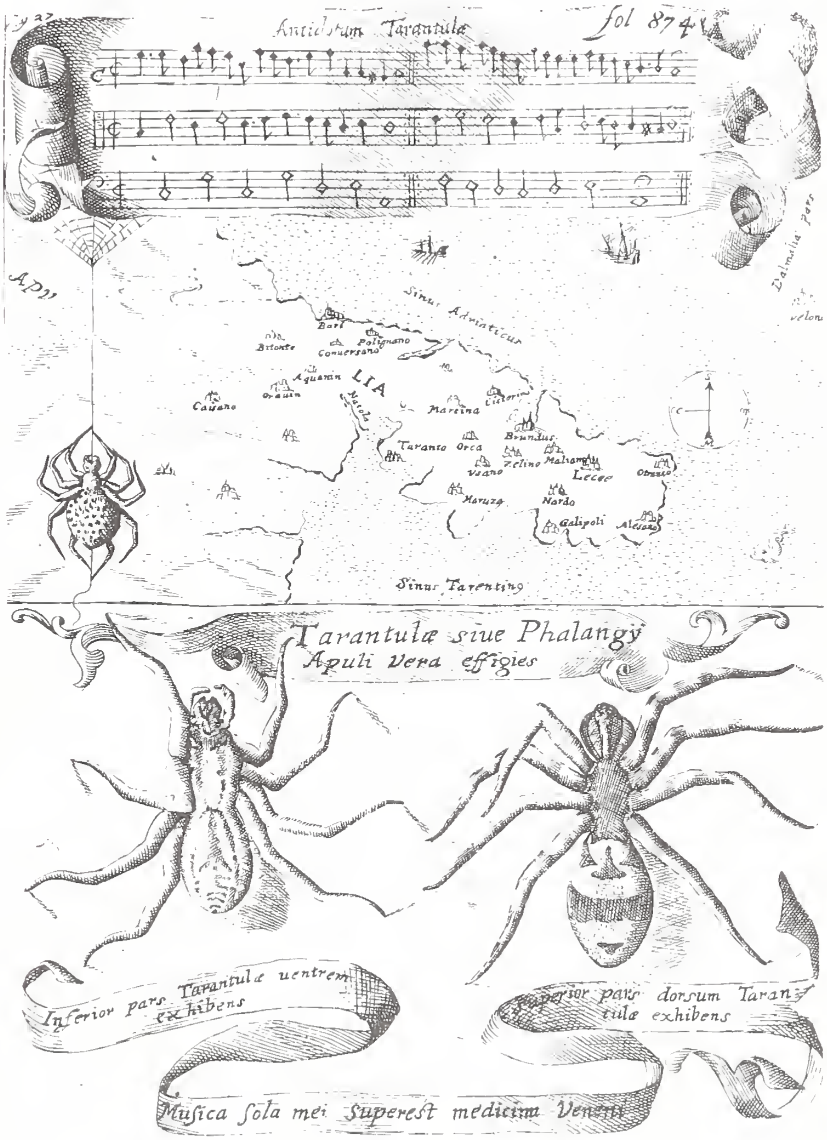
NIH LIBRARY

July 2, and July 4. Tours of the Library, lasting about an hour, are given daily at 1 p.m. No advance reservations are necessary.



From Athanasius Kircher, Magnes; sive, De arte magnetica, 1641. Several examples of tarantellas were preserved by Kircher, a physician and musicologist, in the mid-17th century. This music, when performed, was believed to cure tarantism (supposedly caused by the bite of the tarantula spider) by inducing the victim to participate in a frenzied dance. (NIH Photo # 1591)

(more)

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EXHIBIT (CONT'D)

From Athanasius Kircher, *Phonurgia nova,* *1673. This is a type of tarantella dance. The music, typically involving short phrases played over and over with increasing tempo, induced the tarantism victims to rise from their stupor, sometimes waving swords in the air as they whirled and jumped in a frenzied dance. The dancing would continue for several days, after which the patients appeared to be healed.* (NIH Photo #1592)

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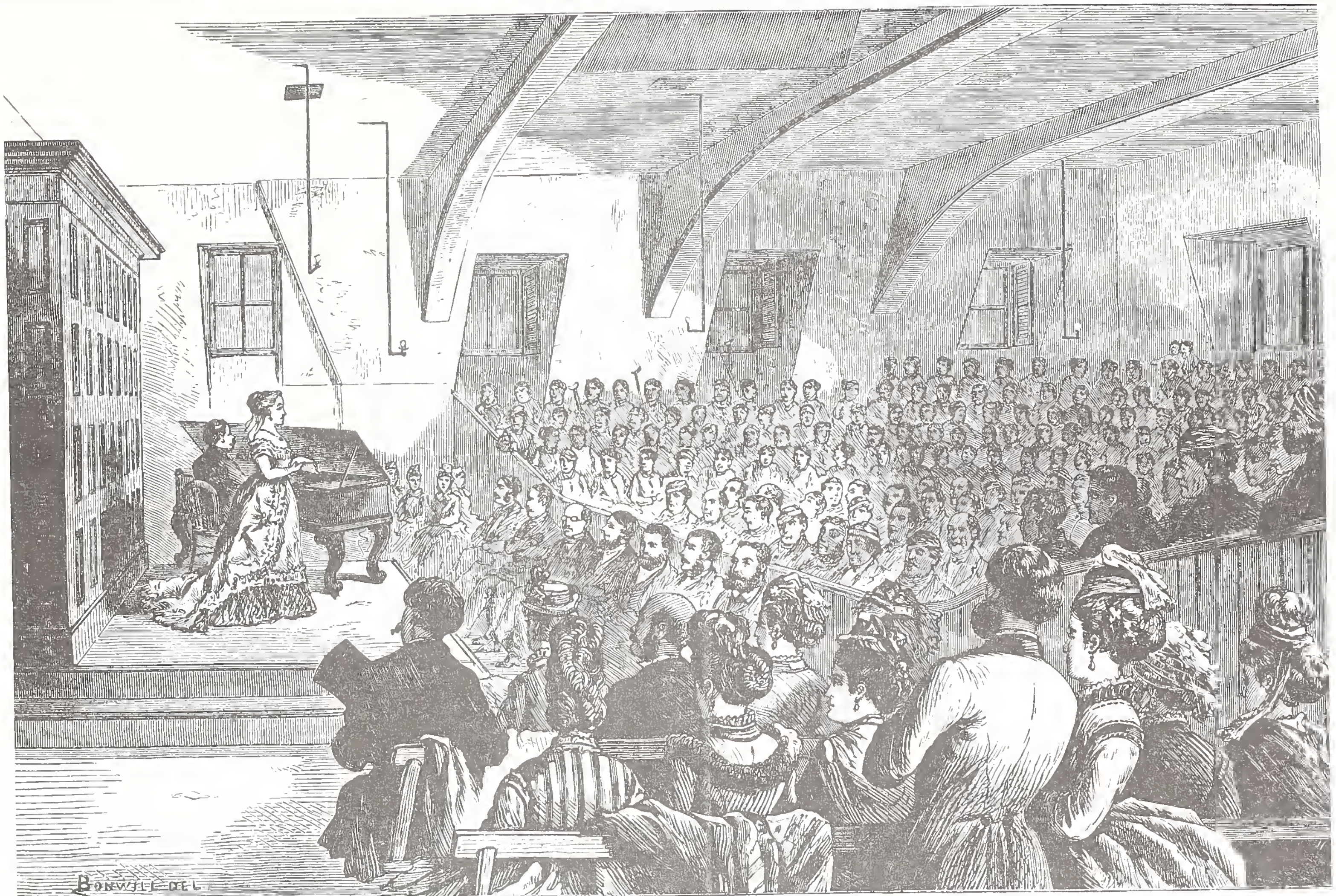
EXHIBIT (CONT'D)


BONWILL DEL.

CONCERT FOR THE INMATES OF THE CHARITY HOSPITAL, BLACKWELL'S ISLAND.—DRAWN BY C. E. H. BONWILL.—[SEE PAGE 150.]

Wood engraving from Harper's Weekly, 1874. This shows one of a series of Friday night concerts provided for mental patients of the Charity Hospital, Blackwell's Island, New York. (NIH Photo # 1593)

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NEWS & FEATURES From NIH

May 1977

News Feature

PROGRESS IS MADE IN UNDERSTANDING LACK OF IMMUNITY TO SOME GONORRHEA

Only patients with long-term or severe gonorrhea are likely to develop antibodies capable of killing the organisms causing the disease. This finding, by NIH's National Institute of Allergy and Infectious Diseases-funded scientists using a recently developed test, helps to explain the seeming lack of immunity to *Neisseria gonorrhoeae* following primary infection.

The test for bactericidal (bacteria killing) antibody developed for use in this study is a modification of procedures used by other investigators to study immunity to *Neisseria meningitidis* and *Haemophilus influenzae*. Scientists at Boston City Hospital and Harvard tested sera from a small number of: 1) individuals with various types of *N. gonorrhoeae* genital infection, 2) individuals exposed to *N. gonorrhoeae* who did not become infected, and 3) individuals with no history of gonococcal infection.

The investigators found that in persons with gonorrhea the development of antibodies depended upon the length and severity of infection. Prolonged or severe infection with gonococcus correlated with the presence of bactericidal antibodies in about 70 percent of the cases studied; whereas, antibodies were found in less than 31 percent of the patients with uncomplicated gonococcal infection.

Of the five individuals who had been exposed to gonorrhea but were not infected, one (20 percent) possessed antibodies to the strain of *N. gonorrhoeae* isolated from her sexual partner. The antibodies, in this case, may have been the result of a previous gonococcal infection or a cross-reaction of *N. gonorrhoeae* with a meningococcal strain.

According to the Boston scientists, there was only one person who had

(more)

GONORRHEA (CONT'D)

antibodies to *N. gonorrhoeae* in the group of individuals with no history of gonorrhea infection. This individual had been working with *N. gonorrhoeae* in a laboratory setting.

The implications of these results were considered by the scientists in relation to the role of immunity to *N. meningitidis*, since this organism has been studied more extensively. As with the meningococcus, mucosal infection with the gonococcus was associated with the development of serum bactericidal antibody; however, this effect was seen primarily in individuals who had been infected for longer than a month. In addition, the data from this study, as well as others, suggested that whereas a majority of adults have bactericidal antibody to *N. meningitidis*, only a few individuals have bactericidal antibody to *N. gonorrhoeae*. The investigators suggest that the apparent difference in prevalence of antibody may be due to a number of factors including the extent of exposure, failure of carriage to induce antibody, and lack of sensitivity of the gonococcal assay as compared with that of the meningococcal assay. More importantly, perhaps, development of bactericidal antibody in most patients with uncomplicated infection may have been curtailed by early antibiotic therapy.

Other scientists have suggested that antigenic differences in bacterial strains may be significant in the pathogenesis of infection and the development of immunity. Strains that cause severe illness may have antigenic determinants or growth requirements different from those of nonpathogenic strains. The investigators feel that, because of these questions, the role of antibodies in gonococcal infection needs further evaluation.

Dennis L. Kasper, Peter A. Rice and William M. McCormack reported their findings in the February 1977 issue of *The Journal of Infectious Diseases*.

#

May 1977

NEWS & FEATURES From NIH

News Feature

NIDR EVALUATES WAYS TO KEEP FLUORIDE IN MOUTH LONGER

Three new ways that fluoride and antimicrobial compounds can be kept in the mouth and body longer to combat decay more efficiently may develop from current investigations supported by NIH's National Institute of Dental Research.

The Institute is searching for methods to safeguard with fluoride the teeth of millions of individuals who live in places with inadequate fluoride in the water supply. Animal research has recently suggested that fluoride, long recognized as the most effective decay preventive known, accomplishes much of its benefit through local reactions in the mouth. Most antimicrobial agents used for oral diseases also act locally, and therefore new methods developed to retain fluoride in the mouth should be applicable to other decay controlling substances.

A device is being developed which attaches to teeth and is intended to be worn without further attention for six months. It would be a wafer or ribbon consisting of a central layer of a plastic impregnated with fluoride. Each side of the ribbon would be covered by a thin layer of another plastic with a porosity that would control the rate of fluoride release when saliva passes over the device. The supply of the agent is thus continuous and the saliva actually spreads it throughout the mouth.

Such an appliance would ensure that fluoride would be constantly present in the mouth at the optimum levels that would be provided by drinking fluoridated water. Fluoride administered by this method not only would act throughout the body by intestinal absorption, but also would act locally in the mouth because it would be constantly released into the saliva. This device would eliminate the need to remember to take fluoride daily. Moreover, being thin

(more)

FLUORIDE (CONT'D)

and flexible, the appliance should be comfortable to wear.

A second means of prolonging the retention of fluoride in the mouth where teeth must directly withstand the challenge of decay-causing bacterial products involves coating tiny spheres of fluoride with ethyl cellulose for slow release. Then the coated pellets are given an overcoat of an adhesive gum which is designed to keep the fluoride in contact with the teeth for several hours. The investigators have used a spray to apply the dry pellets evenly to the teeth, but hope to develop some other type of application.

A third method is a slow-release tablet which uses current methods on the market for other long-acting preparations. When sucked, the tablet should release 10 to 15 percent of its fluoride into the mouth. The remaining fluoride is designed to be absorbed from the intestine in the course of 18 to 24 hours.

These research developments, still in progress, were reported by Dale B. Mirth, Ph.D., and William H. Bowen, D.Sc., of the NIDR, in Proceedings, "Microbial Aspects of Dental Caries," and *Microbiology Abstracts*.

#

News Feature

UCSF SCIENTISTS USE DIURETIC TO CONTROL LUNG MUCUS

Using a diuretic commonly used in treating heart and kidney patients, researchers at UC-San Francisco have located a mechanism that can control the amount of sticky mucus that accumulates in diseased lungs.

The mechanism, called the chloride ion pump, has never been associated with the membranes along the air passages. The use of drugs to locate and manipulate the chloride pump may help researchers determine whether the malfunctioning of the pump is a fundamental defect of patients with cystic fibrosis or asthma.

Brian Davis, M.D., and his associates working in the laboratory of Jay Nadel, M.D., of the UCSF Cardiovascular Research Institute and Departments of Medicine and Physiology, used sections of canine tracheal epithelia to show that the diuretic, furosemide, may influence the movement of water across membranes into the lungs by its action on the chloride ion pump. Davis presented his findings and those of his co-authors, I. Ueki, M.D., I. Bruderman, M.D., M. Marin, M.D., and Jay Nadel, M.D., at the joint annual meeting of the American Lung Association and the American Thoracic Society, May 17, 1977, in San Francisco.

According to Dr. Davis, the drug appears to work just below the layer of cells lining the air passages of the lung. At this site, water begins to move across the layer of cells out into the passages. The amount of water determines whether the mucus is easily removed or whether it becomes sticky and clogs the passages.

Dr. Davis explained that cells use their energy to set up gradients, or different concentrations, of ions across their walls. When the water from

(more)

MUCUS (CONT'D)

underlying blood vessels comes in contact with the ion gradients, they conduct the water across the cell and out into the air passages.

The water released by the cell spreads over the lining of the air passages and forms a thin watery layer below the mucus. In normal lungs, the jelly-like globs of mucus are easily swept along towards the mouth by the continuous beating motion of cilia, the hairlike projections lining the air passages.

Dr. Davis said that when the level of the watery layer falls, the globs of floating mucus drop onto the cilia and slow the sweeping process. In diseases like asthma and cystic fibrosis, the mucus becomes sticky, and the tiny air passages are clogged, which makes breathing very difficult.

Two other drugs tested by Dr. Davis and his colleagues were acetylcholine, a chemical produced by nerves, and histamine, which is released by the body in the allergic reaction. Both of these were shown to increase the chloride ion movement, and hence the amount of water.

Their work was sponsored in part by the Cystic Fibrosis Foundation and NIH's National Heart, Lung, and Blood Institute.

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NEWS & FEATURES From NIH May 1977

News Feature

NIH SCIENCE WRITERS SEMINAR: RESEARCH ON THE GASTROINTESTINAL SYSTEM

Diseases of the gastrointestinal tract are among the most common illnesses in this country, affecting nearly 18 million Americans. Seminar participants will describe various research approaches to gastrointestinal diseases under study at the National Institutes of Health.

Tuesday Morning -- June 7, 1977
9:30 a.m. to 12:00 noon

National Institutes of Health
Building 31-B, B1 Level, Conference Room 5
Bethesda, Maryland

****

Moderator: Edward D. Korn, Ph.D., Chief, Laboratory of Cell Biology, NIH National Heart, Lung, and Blood Institute.

I. Gastrointestinal Hormones.
Jerry D. Gardner, M.D., Chief, Section on Gastroenterology, Digestive Diseases Branch, NIH National Institute of Arthritis, Metabolism, and Digestive Diseases.

II. Immunologic Disease of the Gastrointestinal Tract.
Warren Strober, M.D., Head, Immunophysiology Section, Metabolism Branch, NIH National Cancer Institute.

III. Current Status of the Treatment of Acute Liver Failure.
Paul D. Berk, M.D., Acting Chief, Digestive Diseases Branch, NIH National Institute of Arthritis, Metabolism, and Digestive Diseases.

****

PRESENTED BY THE INTRAMURAL SCIENTISTS OF THE NIH
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(more)

GASTROINTESTINAL HORMONES.

Abstract (of presentation on June 7, 1977)

Jerry D. Gardner, M.D.

In the early 1960's only 3 gastrointestinal hormones were known--secretin, gastrin, and cholecystokinin. Since that time the number identified has increased more than 6-fold in the exploding field of gastrointestinal (GI) hormone research. Twenty GI hormones are now postulated. In some instances they have been identified and characterized only from tissues of lower animals, but theoretically all are present in higher animals, including man.

The striking advances in this field were made possible by availability of the hormones in pure form. This was due in turn to progress in protein chemistry--advances in chromatography, isoelectric focusing, and multi-dimensional electrophoresis--and the development of radioimmunoassays for these gastrointestinal peptide hormones. Dr. Gardner will discuss the history of this research, highlighting recent advances, and theorizing on the mechanisms of action of some of these hormones.

(more)

May 1977

NEWS & FEATURES From NIH

IMMUNOLOGIC DISEASE OF THE GASTROINTESTINAL TRACT.

Abstract (of presentation on June 7, 1977)

Warren Strober, M.D.

Among the 46 human chromosomes, chromosome No. 6 contains the major histocompatibility complex which includes genes that influence immune responses. One gene in this complex is associated with a gastrointestinal disease that demonstrates new information on the workings of the immune system. HLA-B8 is the gene associated with celiac sprue, more aptly called gluten-sensitive enteropathy (GSE). The disease affects about 40,000 persons in the U.S. More than 60 GSE patients have been studied at NIH. The disease is characterized by faulty food absorption, related to a flattening of the intestinal villi (projections) which decreases the intestinal absorptive surface. The antigen or chemical that triggers the disease in susceptible persons is a protein called gliadin, a component of gluten found in wheat. Diets that exclude bread can control most cases of the disease.

Research by Dr. Strober and colleagues suggests that the disease occurs among susceptible persons when ingested gliadin proteins interact with genetically-determined receptors on cells in the intestinal wall of GSE patients. Such receptors are the product of the HLA genes mentioned above. The gliadin/receptor interaction leads to the production of anti-gliadin antibodies, which in turn combine with gliadin attached to receptors on villus epithelial cells. This ultimately leads to the destruction of the intestinal villi. Dr. Strober estimates that 20% of the diseases of the gastrointestinal tract have an immunologic basis. He will report on the GSE studies, then briefly discuss other GI diseases with immunologic aspects, including ulcerative colitis, Crohn's disease, immunodeficiency diseases of the GI tract, pernicious anemia, and allergic diseases of the GI tract.

(more)

May 1977

NEWS & FEATURES From NIH

CURRENT STATUS OF THE TREATMENT OF ACUTE LIVER FAILURE.

Abstract (of presentation on June 7, 1977)

Paul D. Berk, M.D.

Conservative management of fulminant liver failure is unsatisfactory, and leads to an average mortality of approximately 80%. As a result, there is considerable interest in the development of liver assist devices which might function to support life until sufficient hepatic regeneration has occurred to sustain survival. The main approaches currently under study involve dialysis through a variety of special membranes, perfusion of blood through various sorbents (charcoal, synthetic resins, affinity chromatography gels, immobilized hepatic microsomes or microsomal enzymes), or passage of blood over living, functional hepatic cells. Devices employing each of these approaches are undergoing clinical and/or animal trials.

While the technology is impressive, there have been no major conceptual advances since the late 1950's and early 1960's, when all of these approaches were suggested or introduced. Development of both hardware and treatment schedules is largely empirical, as the fundamental biochemical defect(s) requiring correction have not yet been identified. Furthermore, lack of suitably controlled trials has made evaluation of clinical results difficult. As an example, the effectiveness of charcoal hemoperfusion remains uncertain, despite treatment of more than 100 patients by this technique.

Further fundamental research on pathogenesis and pathophysiology, as well as more carefully controlled clinical evaluation of new devices, appear to be the essential ingredients of real progress. A suitable animal model of fulminant liver failure would be an extremely valuable tool for investigators in this area.

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June 1977

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Research Advances

SEXUALLY TRANSMITTED ORGANISMS ARE CAUSE OF ACUTE EPIDIDYMITIS

In young men, sexually-transmitted organisms which cause urethritis (inflammation of the urethra) may also lead to acute epididymitis, an inflammation of the elongated, cordlike structure along the posterior border of the testis. This is the finding of investigators working out of the University of Washington, the U.S. Public Health Service, and the Seattle-King County Health Department in Seattle. In contrast, these researchers found that coliforms and Pseudomonads are the major causes of epididymitis in older men. The research is supported by NIH's National Institute of Allergy and Infectious Diseases.

Since the discovery of drugs effective in destroying gonococcal or tubercular organisms or suppressing their growth, gonococcal and tuberculous epididymitis have become less common. However, epididymitis of unknown origin still occurs frequently. Discovery that non-gonococcal urethritis (N.G.U.) is present in many patients with idiopathic epididymitis suggested an infectious cause of epididymitis to the Seattle investigators; therefore, they undertook to explore the association of acute epididymitis with those agents implicated as causes of N.G.U.

Twenty-four men with symptoms suggestive of acute epididymitis were referred to the investigators from two venereal disease clinics and the U.S. Public Health Service Hospital in Seattle during an eight-month period in 1972-73. Six men were over 45 years old, and the remaining 18 were under 32. All had symptoms

(more)

of epididymitis of less than a month's duration and had received no antibiotics within the preceding month. Each man was examined and diagnosed as having epididymitis on the basis of tenderness and swelling. Each underwent urethral and urine cultures for *Neisseria gonorrhoeae*, *Ureaplasma urealyticum*, herpes-simplex virus, *Chlamydia trachomatis*, cytomegalovirus, and gram-negative aerobic bacteria.

In five of the six over 45 years old, coliform or Pseudomonads were isolated from the urethra discharge or urine. However, 13 (72 percent) of the 18 men aged less than 32 were infected with *C. trachomatis* and/or *N. gonorrhoeae*. Urethritis was present in all but one of these men. As for the five men who were not infected with *N. gonorrhoeae* or *C. trachomatis*, *U. urealyticum* was recovered from the urethra of three of these individuals.

These findings suggest to the investigators that acute non-tuberculous epididymitis in older men is usually associated with coliform or Pseudomonad bacteria in the urine, perhaps associated with inflammation of the prostate gland; whereas, in younger men it is usually associated with urethritis caused by sexually-transmitted agents, including *N. gonorrhoeae*, *C. trachomatis*, and possibly *U. urealyticum*.

However, the Seattle scientists indicate that the relationship of urethritis to epididymitis needs further clarification. They suggest that future investigations of the causes of acute epididymitis should be broadened to include study populations other than patients in a V.D. clinic and should include quantitative, as

(more)

EPIDIDYMITIS (CONT'D)

well as qualitative, cultures of *U. urealyticum.* In addition, they state that further understanding of the pathogenic role of *C. trachomatis* and *U. urealyticum* in epididymitis would be improved by simultaneous sampling of the urethra and epididymitis and that controlled trials of antimicrobial agents might provide further support for an infectious cause of non-specific epididymitis.

This study was reported in the April 16, 1977, issue of *The Lancet* by Drs. James P. Harnisch, E. Russell Alexander, Richard E. Berger, George Monda and King K. Holmes.

#

EFFECTIVE TREATMENT OF LIVER FAILURE IS NOT YET POSSIBLE

Effective treatment of acute liver failure is not at hand, despite a few optimistic reports on small numbers of patients by pioneering clinicians in the field. This conclusion was drawn by an NIH scientist speaking at a NIH Science Writers Seminar on June 7, 1977.

Paul Berk, M.D., of NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases, said that some members of the public and some physicians have been led to believe that successes in treating acute liver failure, as achieved in kidney failure, are just around the corner.

Dr. Berk, chief of the Institute's Section on Diseases of the Liver, said that acute fulminating liver failure remains fatal in approximately 80 percent of cases. The mortality rate is discouragingly high, he added, whether the acute liver failure is due to viral hepatitis, adverse reactions to drugs, exposure to toxic chemicals, or some other cause.

The NIH investigator reviewed the many approaches past and present taken to restore the comatose, critically ill patient with acute liver failure to consciousness. Methods include removal of potential toxins from the blood by dialysis through a variety of special membranes, perfusion of blood through various sorbents (charcoal, synthetic resins, affinity chromatography gels, immobilized hepatic microsomes or microsomal enzymes), or passage of blood over living, functional hepatic cells. Some investigators, notably

(more)

in Japan, have combined several of these approaches in a single, complex device.

Investigations of charcoal columns for hemoperfusion of patients with kidney failure were pioneered by H. Yatzidis, M.D., in Athens, Greece, and T.M.S. Chang, M.D., in Montreal. Later, Dr. Chang was the first to use such an approach in acute liver failure, but studied it only in two patients. The most extensive studies have been done by Roger Williams, M.D. and colleagues, Kings College Hospital, London, in collaboration with the Smith & Nephew company. Their efforts to solve the problem of acute liver failure by passing the patient's blood supply through a charcoal column initially appeared highly promising. As greater numbers of patients were treated, however, the mortality rate became unacceptably high and the study was temporarily terminated.

The same approach has been attempted in the United States at several centers. The U.S. results, although hard to evaluate, appear no more successful than those achieved in London. Difficulties in interpreting the U.S. results are due in part to the nature of the patient population studied, which included some patients with chronic liver failure. In chronic liver failure such as occurs with alcoholic liver disease, there is a 50 percent likelihood of recovery from any particular episode of coma, following conservative treatment, contrasted with the 20 percent recovery rate achieved in acute liver failure.

A later approach to dialysis for liver failure originated in France with the Rhone Poulenc company. The newer device incorpor-

(more)

LIVER (CONT'D)

ated a type of filtration membrane that permitted passage of larger molecules than possible with previous membranes. It was first tested clinically by Pierre Opolon, M.D., in Paris, then by Dr. Williams and his group in London. The results have differed somewhat, with higher survival rates being reported in London. The divergent results, Dr. Berk speculated, may be due to differences in age, sex, and precipitating causes among the patients studied, and to differing components of the intensive care they received during hospitalization. Randomized, controlled clinical evaluations were not done.

Dr. Berk recalled that in the late 1950's and early 1960's, a few attempts were made to treat acute liver failure with the same equipment employed at that time in kidney dialysis. Despite the gaps then and now in scientific knowledge about the liver and acute liver failure, three of six patients treated at three separate institutions in this manner survived. Dr. Berk stated that, with the lack of success achieved by other approaches, a controlled, randomized clinical trial of conventional dialysis equipment might be considered. As is now widely accepted, randomized controlled evaluations of all treatments are essential to accurately assess effectiveness.

Equally important, he said, is the acquisition of fundamental knowledge about the liver and its functioning in health and disease. Unlike the situation with kidney failure, even the toxic body chemicals requiring filtration and removal in acute liver failure have not yet been identified. For instance, bile pigments causing

(more)

LIVER (CONT'D)

jaundice are viewed by some scientists as toxic; others see them as an inconsequential side-effect.

In an effort to develop an animal model of acute liver failure so that its mechanism might be understood, Dr. Berk's laboratory is collaborating with scientists of NIH's Veterinary Resources Services, Division of Research Services, and with biochemists at the National Institute of Mental Health and at NIH's National Institute of Child Health and Human Development. Studies are underway to identify toxic materials, and the rates at which they should be removed from brain and other tissues when the liver is not functioning.

#

Research Advances

NIH SEMINAR EXPLORES ROLE OF GASTROINTESTINAL HORMONES

Recent information on the role of gastrointestinal hormones in controlling the flow of digestive enzymes, maintaining normal acid/alkali secretions, and integrating contraction and relaxation of the bowel was described June 7, 1977, at an NIH Science Writers Seminar by a scientist of NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases.

Jerry D. Gardner, M.D., Chief of the Institute's Section on Gastroenterology, noted that the upper gastrointestinal (GI) tract is probably the major source of peptide hormones. In the early 1960's, he said, only three GI hormones--secretin, gastrin, and cholecystokinin--were known. Since then the field has expanded rapidly. Now, for example, at least six molecular forms of gastrin have been identified in human plasma by scientists in Los Angeles, Liverpool, and Copenhagen.

In addition to the six gastrins, secretin, and cholecystokinin, many other hormones (or candidate peptide hormones) secreted by or influencing the gastrointestinal tract have been identified by scientists at the Karolinska Institutet in Stockholm, the University of Kansas, the Imperial Chemical Industry in England, and the Institute of Medical Pharmacology in Rome, Italy. These peptides include the misnamed vasoactive intestinal peptide (VIP), gastric inhibitory peptide (GIP), motilin, urogastrone, pancreatic polypeptide, and five GI-influencing hormones of lower animals. The latter are caerulein, bombesin, litorin, physalaemin, and eledo-

(more)

isin--the first four from frog skin, and the last from a Mediterranean octopod. All of these hormones are now postulated to be present in man, Dr. Gardner said. He added that the striking advances in the field became possible with the availability of the hormones in pure form.

This he attributed to research payoffs in three fields. In the first, protein chemistry, the relevant advances were in chromatographic separation of the hormones from their tissue sources, isoelectric focusing, and multi-dimensional electrophoresis, providing hormones free of contamination.

The second area of rapid advance has been in the development of radioimmunoassays for the gastrointestinal hormones. Sensitive tests for gastrin were developed by James McGuigan at the University of Florida, Gainesville, based on techniques originally described by Solomon A. Berson and Rosaline S. Yalow working at the Bronx Veterans Administration Hospital. By contrast, radioimmunoassays for gastrointestinal hormones other than gastrin are not yet developed to the point of simple application and evaluation of results.

The third area, efforts to clarify the biochemical basis of action of the GI hormones, is a subject of research in Dr. Gardner's laboratory. He suggested that these fundamental studies might eventually have application in the diagnosis and treatment of gastrointestinal disorders.

#

Research Advances

NCI SCIENTISTS SEEK A BETTER UNDERSTANDING OF CELIAC SPRUE

Research by a scientist of NIH's National Cancer Institute is contributing to an understanding of unique genetic and immunologic conditions that underlie a rare disease, celiac sprue, chiefly affecting the small intestine.

Warren Strober, M.D., Head of the Immunophysiology Section of the National Cancer Institute, described to an NIH Science Writers Seminar on June 7, 1977, research at NIH that links the disease to a defect in the HLA-B8 and associated genes located on human chromosome number 6.

Celiac sprue, more aptly named gluten-sensitive enteropathy (GSE), is a disease characterized by faulty food absorption, related to a flattening of the intestinal villi (projections that aid in absorption). The antigen or chemical that triggers the disease in susceptible persons is the protein gliadin, a component of gluten found in wheat. Diets that exclude bread can control most cases of the disease.

An estimated 40,000 persons in the U.S. have GSE, inherited as a gene defect from both parents. Many times that number are carriers of the trait. A simple immunologic test developed by Dr. Strober and his colleagues will identify carriers as well as those who have GSE, with its associated diarrhea, weight loss and malnutrition.

In studies of 60 patients at NIH's Clinical Center, Dr. Strober found that GSE patients' special genetic inheritance produces unique

(more)

CELIAC SPRUE (CONT'D)

receptors for gliadin on their white blood cells and probably on villus epithelial cells as well. The disease occurs when ingested gliadin proteins interact with the genetically-determined receptors on those cells in regions called Peyer's patches on the intestinal wall of GSE patients. (These protein receptors may be the products of the HLA-B8 and associated gene region.) It is postulated that this interaction leads to the production of anti-gliadin antibodies. These in turn combine with gliadin attached to receptors on the villus epithelial cells, leading ultimately to destruction of the intestinal villi.

Dr. Strober points to GSE as an extraordinary model for studying a genetic disease that operates through the immune system, normally a source of protection from disease. In GSE, the reverse is true.

He also suggested that the HLA-B8 gene is not exclusively responsible for GSE. He postulates that another gene, not linked to HLA-B8 and perhaps on another chromosome, must also be present for GSE to occur. Further studies to test this postulate are underway in his laboratory.

In addition to reporting on GSE, Dr. Strober briefly discussed other disease of the gastrointestinal tract that have an immunologic basis.

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NEWS & FEATURES From NIH

June 1977

Photo Feature

HEW NAMES 17 MEMBERS TO NATIONAL COMMISSION ON DIGESTIVE DISEASES

HEW Secretary Joseph A. Califano, Jr., has announced the appointment of 17 members to the National Commission on Digestive Diseases.

The Commission was established by the October 1976 Amendments to the Arthritis, Diabetes, and Digestive Diseases Act (PL 94-562).

Digestive diseases are among the most common illnesses in the country, affecting more than 18 million Americans. Because they tend to be chronic, such diseases have an enormous economic impact in terms of direct medical costs and time lost from work.

In addition to the 17 public members, the Commission will include the Director of the National Institutes of Health (NIH) and the directors of various NIH Institutes and other Federal agencies which are involved in digestive disease research.

The Commission will deal with a wide range of problems, including investigation into the incidence and duration of digestive diseases, the mortality rates resulting from such illness, and the social and economic impact of these disorders.

Other duties involve an evaluation of public and private facilities and resources for the diagnosis, prevention, treatment of, and research in such diseases, and identification of existing programs which are effective in improving the management of digestive diseases.

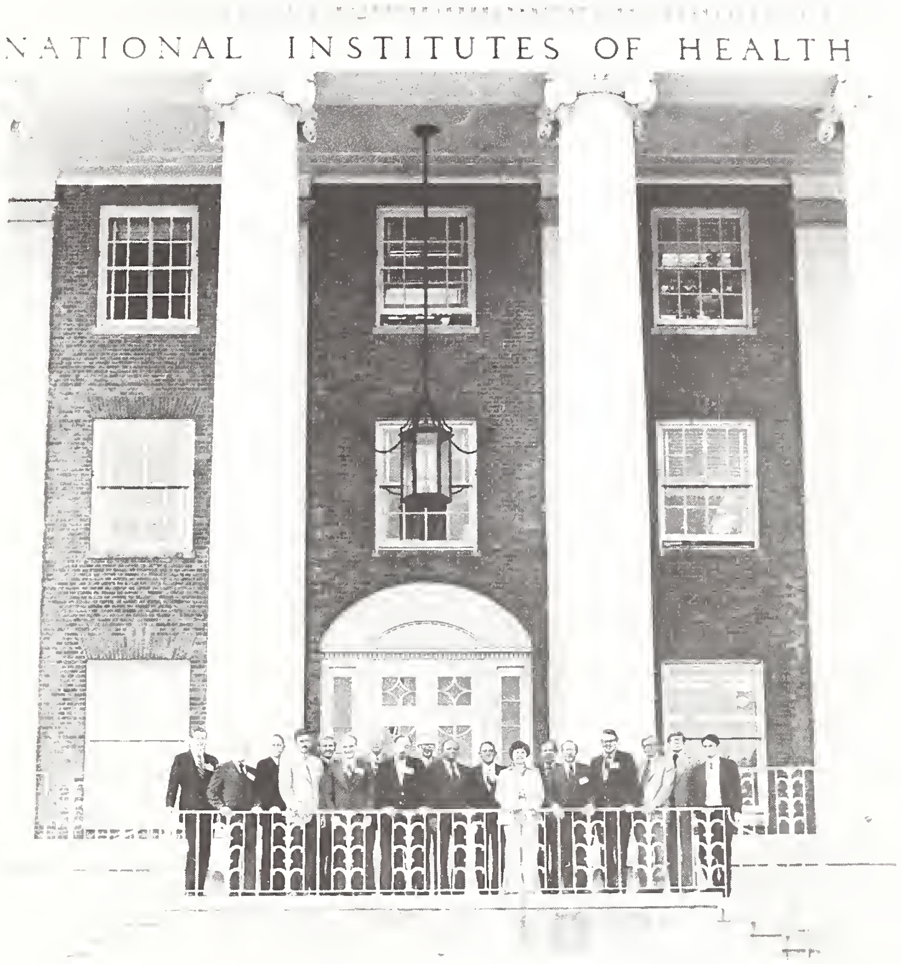
Following this study, the Commission will formulate a long-range plan for the use and organization of national resources to

(more)

COMMISSION (CONT'D)

deal effectively with digestive diseases. The final report of the Commission will be presented to the Congress.

Eugene D. Jacobson, M.D., Associate Dean of the College of Medicine, University of Cincinnati, will serve as chairman of the Commission.



Most of the members of the National Commission on Digestive Diseases were available to pose on the steps of N I H Building One. The members of the Commission will hold public meetings in various American cities. According to a recent schedule, the Commission will be in New York, N.Y.,/Newark, N.J., in early September; in Seattle, Wash., in early October; in Chicago, Ill., in early November; and in West Palm Beach, Fla., in early December. More information about the Commission's schedule is available from the N I H News Branch, Building 31-2B10, Bethesda, MD 20014. (N I H Photo #1594)

(more)

COMMISSION (CONT'D)

Eugene D. Jacobson, M.D. (center), is shown sharing his ideas about the National Commission on Digestive Diseases with other members of the Commission. Dr. Jacobson was elected chairman of the Commission on April 11. (N I H Photo #1595)

(more)

COMMISSION (CONT'D)

Several Commissioners turn to listen as a member of the audience is given an opportunity to comment about the plans of the National Commission on Digestive Diseases. (N I H Photo #1596)

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NEWS & FEATURES From NIH

June 1977

News Feature

SECOND VIRUS IS SUSPECTED IN NON-A, NON-B HEPATITIS

A second unidentified virus may be responsible for some cases of a major type of viral hepatitis, currently designated "non-A, non-B". This finding by scientists at the University of Southern California School of Medicine and at NIH's National Institute of Allergy and Infectious Diseases (NIAID) comes out of studies of patients with multiple attacks of hepatitis. It extends previous evidence that an unidentified virus is associated with cases of post-transfusion hepatitis unrelated to hepatitis A or B viruses, the commonly recognized agents of the disease.

Since the 1940's scientists have recognized that two different viruses are responsible for two forms of viral hepatitis, hepatitis A and B. More recently, a third form of hepatitis, "non-A, non-B", has been suspected, since thousands of post-transfusion cases have appeared to be unassociated with either of the known viruses. Scientists understand very little about the virus or viruses responsible for this so-called "non-A, non-B" hepatitis, but previous epidemiologic and serologic evidence has pointed to the existence of at least one "non-A, non-B" hepatitis virus.

Although none of the hepatitis viruses has been isolated, the discovery of viral antigens as markers of infection has permitted the diagnosis of hepatitis A and B and visualization by the electron microscope. As no viral antigens have been associated with "non-A, non-B" hepatitis, this type of hepatitis is diagnosed only by the lack of serologic evidence, viral antigens and antibodies, for hepatitis A and B.

(more)

Patients with multiple acute attacks of viral hepatitis have been the most puzzling to diagnose. Although one bout can usually be identified as hepatitis B, the cause of the other episodes has often been conjectural. Before the development of immune electron microscopy, a laboratory technique used to detect hepatitis A infection, the non-B episodes were assumed to be hepatitis A. In some instances, other infectious agents or diseases that mimic viral hepatitis, such as infectious mononucleosis, have also been suspected.

To explore the etiology of these non-B episodes, the scientists in the present study serologically tested 13 patients during 30 bouts. Ten patients had two attacks while three had three or four bouts of disease. The investigators found that the hepatitis B virus was associated with one attack in 12 of the 13 patients. Hepatitis A, on the other hand, was the cause of only one episode in two patients.

In addition, no patients had more than one attack characterized as hepatitis A or B. This left 16 bouts unrelated to either the hepatitis A or B virus. Tests for infectious mononucleosis, caused by the Epstein-Barr virus, and for cytomegalovirus ruled out both these viruses as causes of these "extra" episodes.

Furthermore, the scientists point out that each of the three patients with multiple attacks had two separate episodes of unidentifiable or "non-A, non-B" hepatitis, suggesting the existence of

(more)

at least two, immunologically distinct, "non-A, non-B" hepatitis viruses.

Since serologic tests for hepatitis A and B are highly reliable, the researchers believe it unlikely that multiple attacks are actually undetected hepatitis A or B infections. The scientists also claim that circumstances refute interpretation of these multiple attacks as recurrences of an initial chronic infection with A or B. All patients were in good health before each bout, suggesting the onset of separate infections. Also, symptoms and even biopsies were typical for acute viral hepatitis. Although chronic hepatitis occasionally mimics acute hepatitis, it rarely does so repeatedly. In addition, during the "non-A, non-B" episodes there was no significant change in the serologic measurements for hepatitis A or B, making resurgence of a chronic infection unlikely.

Based on these considerations, they conclude that viral hepatitis is caused not only by the two recognized viruses, but also probably by two, immunologically distinct "non-A, non-B" viruses, as well.

The report of this research by James W. Mosley and Allan G. Redeker from the University of Southern California School of Medicine, Los Angeles, California, and S.M. Feinstone and R.H. Purcell from NIAID, appeared in the *New England Journal of Medicine*.

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Photo Feature

LEAD MAY ACCUMULATE IN FETUS OF PREGNANT WOMEN WHO SMOKE

Cigarette smoking during pregnancy causes lead to accumulate in the fetuses of smoking mothers as well as in the mothers themselves, according to researchers working in the Perinatal Clinical Research Center at Cleveland Metropolitan General Hospital. The Cleveland research indicates for the first time a direct correlation between increased lead in smoking mothers and lead found in their infants, according to Dr. Mortimer Rosen, principal investigator at the center.

The Perinatal Clinical Research Center, one of 83 such units supported by NIH's Division of Research Resources, is a miniature research hospital within the larger Cleveland Metropolitan General Hospital, providing highly specialized clinical research facilities to the entire medical staff of the institution.

According to Dr. Rosen, the research performed by Drs. Paul and Betty Kuhnert, members of the center investigative team, originally looked at the problem of lead accumulation in pregnant women who lived in industrialized urban areas. This study found that the lead accumulation in both the mothers and fetuses was high enough to cause inhibition of the enzyme aminolevulinic acid dehydratase (ALAD), an enzyme which helps red blood cells make hemoglobin. The investigators then looked specifically at those mothers who smoked and found that cigarette smoking can cause additional lead accumulation in both the mothers and their infants.

Drs. Kuhnert report that the infants' blood lead levels were

(more)

always less than the mothers' levels, but that the lead in the infants increased in direct proportion to the levels found in the smoking mothers.

The investigators determined the blood lead levels of the mothers and their infants and correlated them with the inhibition of the enzyme ALAD. ALAD is extremely sensitive to lead and therefore usually is affected by lead long before other body substances. The researchers carefully measured the activity level of ALAD in the red blood cells of pregnant women and their fetuses.

"These measurements showed that the inhibition of ALAD was greater in smoking mothers and their infants than in nonsmoking mothers and their infants. This inhibition apparently is due to increased blood lead levels," Dr. Paul Kuhnert says.

"Pregnant women who smoke expose themselves and their infants to higher concentrations of lead than exist in their environments. This increased exposure results in decreased activity levels of ALAD. It also may be inferred that lead may inhibit the activity of ALAD in other body tissues, such as the liver and kidneys where it helps synthesize other hemoproteins."

Although lead can cause brain damage in children, Dr. Rosen syas it is unknown whether the levels of lead found in mothers and their infants due to smoking are high enough to cause any damage. Additional studies are now taking place on the Perinatal Clinical Research Center to determine whether the levels measured represent a significant health hazard.

"One thing is for sure, we know it can't be doing them any good," Dr. Rosen says.

(more)

LEAD (CONT'D)

Smoking during pregnancy can result in the accumulation of lead in both the mother and her fetus, according to a recent study conducted in the Perinatal Clinical Research Center at Cleveland Metropolitan General Hospital. The special research unit is one of 83 such centers funded by N I H's Division of Research Resources. (N I H Photo # 1597)

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News Feature

DENTAL RESEARCHERS CONTINUE STUDIES OF BACTERIA IN MOUTH

Florida scientists have found that two bacteria commonly found in the mouth can grow when saliva alone provides their source of nitrogen. Awareness that decay-causing organisms are also able to multiply when humans are asleep emphasizes the need to dislodge and remove as many bacteria as possible each evening, as well as during waking hours, in order to maintain a healthy mouth. This research is funded by NIH's National Institute of Dental Research.

Both *Streptococcus mutans*, a cause of tooth decay, and *S. sanguis*, believed to be harmless, colonize on teeth and form plaque. Moreover, because each can grow separately in the mouths of rats reared free from other bacteria, it is evident that neither is dependent for its metabolic needs on the ability of other organisms to break down dietary nutrients.

Although it is known that some bacteria living in the mouth can provide for their carbohydrate needs by extracting simple sugars from the complex mucopolysaccharides in human saliva, the scientists were uncertain whether, in the absence of dietary foods, bacteria could multiply when the only available nitrogen was in saliva. This fluid contains limited amounts of the particular free amino acids that bacteria require. If any bacterium could grow independently of human food or other bacteria, it would presumably have an ecological advantage, especially when an individual is sleeping and food is not eaten.

(more)

BACTERIA (CONT'D)

The bacteriologists learned that neither of these streptococci would grow and multiply in a chemically-defined basal medium of glucose, salts, minerals, and vitamins without the nitrogen in protein. However, both would grow if a sterilized protein fraction (molecular weight over 10,000) of saliva was added. A fraction with a molecular weight less than 10,000 barely sustained growth through one transfer.

Although saliva does not contain free cysteine, an amino acid essential for bacterial growth, both streptococci grew on saliva. Therefore, the scientists believe that the bacteria were able to metabolize the salivary proteins to obtain cysteine and other amino acids needed for growth. Amino acid analyses and isoelectric focusing studies of the culture media were made before and after bacterial growth. The findings that certain protein bands disappeared after growth, with a concomitant loss of amino acids, provided evidence that these bacteria were able to use salivary proteins as a source of nitrogen.

The findings by Richard A. Cowman, Ph.D., Robert J. Fitzgerald, Ph.D., Sally J. Schaefer, M.S., Margaret M. Perella, B.S., and Ann H. Cornell, B.S., were reported in *Caries Research.* The studies were conducted at the University of Miami and the Veterans Administration Hospital, Miami.

#

June 1977

News Feature

NEW GUIDELINES ARE DEVELOPED FOR ARTIFICIAL KIDNEY MACHINES

New guidelines for testing and evaluating the safety, performance, and human compatibility of artificial kidney machines have been developed by an interdisciplinary study group drawn from government, industry, and academic and nonprofit research organizations.

The resulting publication, entitled "Evaluation of Hemodialyzers and Dialysis Membranes," was developed under sponsorship of the Artificial Kidney - Chronic Uremia Program, the component of NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases studying ways to improve devices and therapy to aid patients with end-stage kidney disease.

At the present time, 32,000 patients afflicted with irreversible kidney failure, who would otherwise die, are being kept alive with the aid of thrice-weekly artificial kidney treatments. About 95 percent of the cost of this maintenance treatment is born by the Federal government primarily through MEDICARE.

Improvements in dialysis therapy to make the treatment briefer, more effective, and less costly are being pursued vigorously through the Artificial Kidney Program, and these developments should bring about significant human benefits and could result in substantial savings of Federal resources.

The new report is expected to aid considerably the efforts of clinicians, bioengineers, scientists, and manufacturers engaged in the struggle to improve current treatment of end-stage kidney

(more)

MACHINES (CONT'D)

disease. The guidelines will also help officials of the Food and Drug Administration in the task of developing standards for safety and effectiveness of dialysis equipment, required under the new Medical Device Amendments of 1976.

The new, 231-page publication provides detailed guidelines for clinical, toxicological, physical, and chemical testing and quality control of artificial kidney devices, their components, and the water used in them for blood purification. In addition to a discussion of the principles involved and detailed instructions for the various laboratory and clinical tests, the book also encompasses a catalog of the characteristics of available dialyzers and membranes and a broad bibliography of scientific references pertaining to the multitude of test methods involved.

The interdisciplinary study group which authored this publication, comprised of nephrologists, bioengineers, toxicologists, chemists, and physicists, was chaired by Dr. Elias Klein of Gulf South Research Institute.

Copies of the book are available from the Coordinator of the Artificial Kidney - Chronic Uremia Program, National Institute of Arthritis, Metabolism, and Digestive Diseases, NIH, Building 31, Room 9A-07, Bethesda, Maryland 20014.

#

June 1977

News Feature

NIDR DISCUSSES SCHOOL-BASED FLUORIDE PROGRAMS

Self-applied fluoride tablet and fluoride mouthrinsing programs conducted in schools as a means for preventing tooth decay are described in a new publication issued by the National Institute of Dental Research.

Dental caries (tooth decay) is one of the most common diseases of our society. Statistics show that nearly 50 percent of all children under age 15 have never had dental care. The dimensions of the problem of tooth decay and the consequences of this destructive disease make prevention of decay in children's teeth imperative.

Years of research have proved that drinking fluoridated water from birth is the best way to ensure having better teeth for life. Where the fluoride concentration in the drinking water is inadequate, school-based fluoride programs are a practical means of reaching children and achieving a sizable reduction in dental decay.

The new publication, Preventing Tooth Decay: A Guide to Implementing Self-Applied Fluoride Programs in Schools, was developed to assist citizens in initiating these prevention methods in fluoride-deficient school districts or communities. The procedures can be administered with minimal interruption of a school's academic program. Few materials and supplies are required, and the technics of these inexpensive procedures are easy to learn.

The 38-page, easy-to-use Guide provides community leaders

(more)

PROGRAMS (CONT'D)

with outlines for determining the appropriate self-applied fluoride program, sample letters for requesting parental consent, listings of supplies and personnel required, and instructions for conducting the procedures in the classroom setting.

Single copies of the Guide are available without charge from the National Caries Program, National Institute of Dental Research, 549 Westwood Building, Bethesda, MD 20034 (telephone: 301-496-7716). Multiple copies of the Guide are available for purchase from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402, at $1.70 per copy. Remittance must accompany your order.

#

June 1977

News Feature

NIAID PUBLISHES REPORT ON BIOREGULATON OF INSECTS

The National Institute of Allergy and Infectious Diseases has published a conference report entitled "Biological Regulations of Vectors".

The conference was held to provide a forum to report fundamental research leading to more effective methods of bioregulation of insects and other invertebrates that transmit disease agents. The conference also focused on coordination of NIAID-supported bioregulation investigations with those of other agencies and institutions.

Use of microorganisms to control disease vectors is recognized as an important approach to preventing certain tropical diseases. It has become particularly pertinent as chemical methods of pest control have become ecologically unsuitable.

Bioregulation of vectors refers to the manipulation of living agents in a habitat in order to reduce the number of specific disease-transmitting organisms.

Conference participants addressed problems of detecting, isolating and identifying bacteria and fungi for use as agents in biocontrol. Nutrition, growth conditions and mode of action of vectors were emphasized. The conference also focused on those agents which use fermentation as a means of mass propogation.

Copies of the conference report are available through the Superintendent of Documents at the U.S. Government Printing Office, Washington, D.C. 20402. The price of the publication is $2.50. Request Stock Number 017-044-00028-1.

#

June 1977

NIH SURVEYS EMPLOYMENT MARKET IN BIOMEDICINE

News Feature

Dr. Donald S. Fredrickson, Director, National Institutes of Health, has announced that NIH is conducting a survey of employers and trainers of biomedical scientists to assess the current state of the employment market and the prospects for the future.

Academic institutions, industry, and Government agencies are being asked for information on staff positions which have been filled, are presently open, or are expected to become open during the year ending September 30, 1977. The resulting data will be analyzed by Westat Research Inc., the consulting firm assisting NIH in the survey.

In a similar study conducted by Westat in 1975, doctoral level biomedical scientists--as opposed to other scientific fields--were found to be in short supply. Budgeted openings for qualified personnel in that year substantially exceeded the supply of eligible candiates entering the field. The shortage appeared to be greater for candiates with the M.D. degree.

The survey is being coordinated with the work of the National Academy of Sciences committee studying national needs for biomedical and behavioral research personnel. This study was requested by the Congress.

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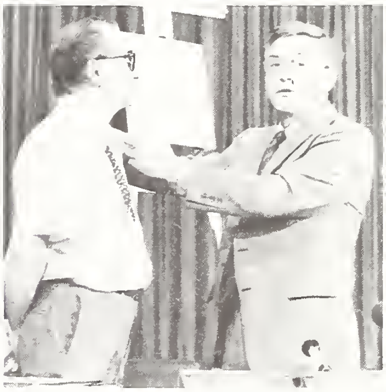

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NEWS & FEATURES From NIH July 1977

Research Advances

HIGHER BLOOD PRESSURE IS FOUND IN WOMEN ON ORAL CONTRACEPTIVES

Women who use oral contraceptives were found to have higher mean blood pressure values than nonusers. Investigators involved in the Kaiser-Permanente Contraceptive Study in Walnut Creek, California found that oral contraceptive users had a slight (5 to 6mm Hg diastolic, 1 to 2mm Hg systolic) but significant statistical rise in blood pressure. This research was supported by NIH's National Institute of Child Health and Human Development.

From January 1, 1969 to December 31, 1972, 13,358 women ranging from 15 to 60 years of age were enrolled in the study. 1,581 participants who took diuretics, cortisone, reducing or antihypertensive medication were excluded from the study. Over a three-year period 9,511 women had two or more examinations and 3,487 women had only one examination. The women were divided into three groups, current user, past user, and never user. Subjects underwent various test procedures and the blood pressure was measured approximately two hours after the examination began.

The effects of other factors such as obesity and age on levels and changes in blood pressure were also assessed. In the influencing of blood pressure levels, it was found that oral contraceptives did not interact with such factors as alcohol consumption, family history of hypertension, and time of examination.

Interestingly, past oral contraceptive users had less high blood pressure than women who had never used oral contraceptives. Subjects who did not begin or resume oral contraceptive use ex-

(more)

CONTRACEPTIVES (CONT'D)

perienced no significant changes in blood pressure values between the first and second examinations. Women who used oral contraceptives at the time of both examinations did not show a significant change in blood pressure values. Subjects who initiated or resumed oral contraceptive use during the study experienced a significant increase (4mm Hg systolic, 1mm Hg diastolic) in blood pressure value.

Blood pressure values shifted uniformly upward for subjects initiating or resuming oral contraceptive use in comparison to those women who did not initiate or resume the use of these drugs. This uniform shift has led the researchers to assume that changes in blood pressure caused by oral contraceptives are roughly the same for all women.

The question still remains as to whether stroke and coronary artery disease are influenced by such a slight rise in blood pressure as that observed among the women in the Kaiser-Permanente Contraceptive Study.

Adverse effects from an increase in blood pressure, particularly the systolic, on the vascular system is well documented. Previous studies have shown that for each 10mm Hg rise in systolic pressure, there is a 30 percent increase in the risk of cardiovascular disease, even in the nonhypertensive group.

Results of this study clearly associates oral contraceptive use with a rise in blood pressure. Women who are already predisposed to the development of cardiovascular disease should be aware that the use of oral contraceptives can present a potential risk

(more)

CONTRACEPTIVES (CONT'D)

factor. This research was reported by Dr. Irwin Fisch and Jess Frank, M.A., in the June 7, 1977 issue of the *Journal of the American Medical Association.*

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Melvonna M. Ballenger, an NIH summer journalism intern, assisted in the preparation of this story.

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RETINAL DISEASES--Diseases of the retina, the light-sensitive tissue at the back of the eye that transmits visual information to the brain, account for more blindness and visual disability in the United States than any other cause, according to the National Institutes of Health.

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Research Advances

HORMONE USE IS LINKED WITH ELEVATED CHOLESTEROL

Hormone use, both of oral contraceptives and menopausal estrogen therapy, has been linked with elevated blood levels of cholesterol and triglyceride. For women in age group 20 to 24, elevated serum cholesterol was related to the use of oral contraceptives in excess of 40 percent of all instances and elevated triglycerides in 60 percent of all instances. A gradual decrease occurs with age, but even in women aged 45-49, there still is in excess of 20 percent of instances of elevated triglycerides associated with hormone use.

These findings were presented by Dr. Herman Tyroler of the University of North Carolina at the Lipid Research Clinic (LRC) press briefing sponsored by the National Heart, Lung, and Blood Institute at NIH on July 13, 1977. The Lipid Research Centers, of which there are 12 situated in the United States and Canada, were established by the National Heart, Lung, and Blood Institute to detect and manage blood lipid (fat) abnormalities as well as to research their prevalence and control.

In this particular prevalence study, which is reported in detail in the July 2 issue of *The Lancet,* the LRC's screened 18,603 women aged 15 and over from a wide range of society. Blood levels of cholesterol were recorded because its positive association with coronary heart disease has been well established. Blood levels of triglyceride, which is the main component of adipose (fat) tissue, were recorded as well. Evidence suggests that triglyceride levels are a separate risk factor in coronary disease, but a positive

(more)

CHOLESTEROL (CONT'D)

association has yet to be proven.

The press briefing presented other results from the Lipid Research Clinics including:

* Socio-Economic Correlations -- In a survey of some 15,000 adults, men and women employed in higher occupations and with higher educational attainment had slightly lower cholesterol and substantially lower triglyceride levels. This is a complete reversal of the findings of earlier surveys which correlated high status with high cholesterol. These present results may reflect a growing awareness, particularly among the better educated, of the role of lipids in coronary disease.

* Lipid Distribution -- Comparison of the LRC cholesterol distributions with those of previous studies suggest that there has been a slight fall in cholesterol levels in the U.S. populations consonant with nutritional findings and of possible significance in the reduced coronary mortality figures reported for the U.S.A.

An LRC study of 20,000 children aged 0 to 19 has identified a significant drop in cholesterol levels during adolescence. The cause of this drop is not certain and further research may help clarify some of the mechanisms which regulate cholesterol levels.

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Research Advances

NCI PUBLIC EDUCATION PROGRAM CONCERNS THYROID CANCER RISKS

A program to inform the professional community and the general public about irradiation-related thyroid cancer was announced July 13, 1977, by Dr. Guy R. Newell, Acting Director, National Cancer Program, National Cancer Institute.

The goals of the educational program are twofold: to brief physicians on how to examine, diagnose and treat irradiation-related thyroid tumors; and to urge the special population in the United States that is at increased risk of developing thyroid cancer to be examined by a physician.

For several decades beginning in the early 1920's thousands of individuals in the United States received X-ray treatments for a number of noncancerous conditions, particularly in the years before antibiotics became available. Radiation therapy was considered good medical practice and effective treatment for such conditions as ringworm of the scalp, enlargement of the thymus gland, deafness due to lymphoid tissue around the Eustachian tubes, enlargment and inflammation of the tonsils and adenoids, and acne. Short-term effects of these treatments appeared to be excellent.

In recent years, however, a link has been recognized between tumors of the thyroid gland and X-ray treatments administered 5 to 40 years previously to the head, neck or upper chest. Only a small proportion of irradiated individuals have developed thyroid tumors, and most of these tumors have been benign,

(more)

RISKS (CONT'D)

Those that are cancerous usually remain confined to the neck for long periods and can be successfully removed surgically.

A nodule (a small rounded eminence) that can be felt on the thyroid gland, a mass in the neck of increasing size, or a history of persistent hoarseness or difficulty in swallowing may indicate the presence of a tumor.

In the inital diagnosis of a thyroid tumor, inspection and palpation (feeling with the fingers) are the two essential steps taken by a physician. Inspection, especially on swallowing, may reveal a mass or lack of symmetry in the neck that might be overlooked by palpation alone. Palpation of the thyroid gland, the cervical lymph nodes and salivary glands (because these may also develop tumors) is done with great care.

Because of the mobility of the U.S. population and the widespread use of irradiation therapy for many head and neck ailments, individuals now at increased risk of thyroid tumors may live anywhere in the country and may range in age from 5 years to almost 60.

Two publications are being widely distributed by the National Cancer Institute (NCI), as the initial step in making information available to professionals and the general public:

- * Information for Physicians: Irradiation-Related Thyroid Cancer;
- * Information for the General Public--Did You, As A Child

(more)

RISKS (CONT'D)

or a Young Adult, Have X-Ray Treatments Involving Your Head or Neck?

These publications may be ordered without charge from the Office of Cancer Communications, Department G, National Cancer Institute, Bethesda, Maryland 20014.

Television, radio, and printed media people (above) covered the discussion of thyroid cancer by a panel of experts. Oliver H. Beahrs, M.D., (lower left) was one of the main speakers, and later demonstrated (lower right) how simple, yet important, a thyroid examination is for people thought to be at risk. (NIH Photos #1598, 1599, and 1600)

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Research Advances

COMMUNITY-BASED HEALTH EDUCATION CAN HELP PEOPLE CHANGE LIFE STYLE

Community-based health education which relies heavily on the mass media can persuade people to change their life style and to improve their health status, according to a three-year Stanford University study.

Results of the study, which was funded by NIH's National Heart, Lung, and Blood Institute "strongly suggest that mass media campaigns directed at entire communities may be very effective in reducing the risk of cardiovascular disease."

The project is the first time that news media have been so extensively involved in a scientific behavior change effort at the community level.

Results are reported in the June 4 issue of *Lancet*, a British scientific journal.

Dr. John W. Farquhar, director of the Stanford Heart Disease Prevention Program, says the project represents the type of preventive effort needed to help stem the epidemic of heart disease which claims the lives of more than 600,000 Americans per year.

"Most deaths of people under 65 in the U.S. due to coronary disease are preventable," he says. "We believe that success in achieving substantial behavior change at the community level lies at the root of any future national campaign to reduce premature mortality from heart disease and stroke."

The study began in 1972 with pre-campaign surveys conducted in three northern California communities--Watsonville, Gilroy and

(more)

Tracy.

The researchers gathered data from about 500 randomly-selected men and women, aged 35 to 59, in each town. They measured knowledge about heart disease risk factors, daily intake of cholesterol, saturated and polyunsaturated fats, sugar, and alcohol, and the daily rate of smoking. They also measured plasma cholesterol and triglyceride concentrations, blood pressure and body weight.

Two follow-up surveys took place at annual intervals. A random sample of residents in Tracy was surveyed each year as a control, but received no media campaign.

Fifteen percent of the Watsonville participant sample, at high risk for coronary heart disease, were selected for more intensive individual and group counseling in addition to the mass media campaign.

From 1972 through 1974, the mass media in Watsonville and Gilroy urged residents to change high risk habits such as cigarette smoking, to improve their diets, and to exercise. The campaign included more than 50 television spots, 100 radio spots, several hours of television and radio programming, newspaper advertisements and stories, billboards, posters, and printed material mailed to community residents. The campaign was conducted in both English and Spanish.

The researchers found that in the control community, Tracy, the risk of cardiovascular disease increased moderately over the two years. In the treatment communities, however, there was substantial and sustained decreases in cholesterol and triglyceride levels and

in blood pressure; fewer respondents reported they smoked; and their knowledge about risk factors increased.

Compared to no treatment, overall risk of cardiovascular disease (heart attack and stroke risk) was reduced 25 percent in Watsonville and 24 percent in Gilroy after two years of the media campaign.

Compared with the control community, systolic blood pressure dropped six to nine percent in the two towns.

In Watsonville, 32 percent of the intensively counseled high risk respondents had given up smoking by the end of the first year, and 44 percent had done so at the end of the second year.

This degree of change in smoking is, according to Dr. Farquhar, "unusually large; particularly since the change occured in a random sample rather than in the usual volunteers for smoking cessation clinics."

The combination of media and face-to-face intensive instruction of high risk subjects in Watsonville was more effective in altering smoking behavior than was mass media alone, according to the *Lancet* report.

The initial improvement was greater in this high risk group, but at the end of the second year the decrease in risk was similar in both treatment communities.

"The mass media," according to Dr. Farquhar, "are potentially much more cost-effective than face-to-face education methods. But we believe that media effects could be considerably enhanced if they could help stimulate and coordinate interpersonal instruction

(more)

programs in natural community groups, such as towns and factories.

"We think our results to date already provide a basis for planning and carrying out community-based risk reduction," says Farquhar.

In future work, researchers hope to find ways to provide such instruction programs and longterm social support in the communities so as to help maintain the changes in life styles already initiated.

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FOOD ALLERGIES--The most common food allergies are to fish, berries, nuts, eggs, cereals, milk, pork, chocolate, beans, and various fresh fruits. The National Institutes of Health reports that some people are also allergic to such substances as food additives.

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Research Advances

IMPORTANCE OF SEX MATCH IN BONE MARROW TRANSPLANTATION IS NOTED

The occurrence of Graft Versus Host Disease (GVHD) and survival of patients with aplastic anemia treated by bone marrow transplantation are strongly influenced by the sex match of the marrow donor and recipient. This is the major finding of researchers at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle, Washington. They reviewed the records of more than 70 aplastic anemia patients who were bone marrow recipients. The scientists have support from NIH's National Institute of Allergy and Infectious Diseases.

Recent studies have indicated that grafting marrow from a HLA-identical sibling is more effective than conventional therapy for the treatment of severe aplastic anemia. However, high mortality is still associated with this procedure and can largely be accounted for by marrow graft rejection and GVHD. The Seattle researchers have been concerned with both of these phenomena. In other investigations, they have found marrow graft rejection to be associated with two prognostic factors: positive *in vitro* tests of sensitization of marrow recipient against marrow donor and a low number of marrow cells used for transplantation. The present analysis was aimed at identifying prognostic factors associated with GVHD and survival of those patients who did not reject their marrow graft, but rather showed sustained marrow engraftment.

Seventy-three consecutive patients with severe aplastic anemia were treated by marrow transplantation from HLA-identical siblings.

(more)

MARROW (CONT'D)

Five of these patients died within eight days following transplantation, too early for meaningful evaluation. In addition, 21 patients rejected their initial graft and only two of them survived. In contrast, the scientists reported there were only 18 deaths among 47 patients who had sustained engraftment. In 16 of these patients, death was associated with GVHD. Twenty-nine of the 47 patients with sustained engraftment were alive with complete hemotologic restoration between 8 months and 5 years at the time this study was reported. Since GVHD was obviously not a problem in patients with graft rejection, the scientists felt that it was reasonable to focus analysis in this study on the group with sustained engraftment.

The Seattle researchers used statistical methods to analyze the pre- and post-transplantation data in order to identify factors that predicted survival. Of the 24 factors entered into the analysis, only two strongly correlated with survival: (a) sex match of the donor and recipient and (b) absence of refractoriness (unresponsiveness) to random donor platelets at the time of transplantation. However, refractoriness adversely influenced only the survival of the sex mismatched patients.

According to the scientists, this data suggests and X and Y associated transplantation antigen systems are important determinants of the outcome of marrow grafts between HLA-identical siblings for the treatment of aplastic anemia. However, they stress that these findings are based on data involving a rather small sample size (47 patients, 18 deaths) and that factors such as

(more)

preceding androgen treatment and age should be more closely monitored in future studies. In addition, the mechanisms by which refractoriness to random donor platelets influence survival is currently unclear.

If confirmed, these findings have some obvious therapeutic implications, e.g. selection of a sex-matched marrow donor if several HLA-identical siblings are available, and early transplantation (a) because of the excellent chances for survival in the case of a sex-matched recipient, and (b) to prevent further deterioration of the chances for survival in the case of a sex-mismatched recipient by avoiding the development of refractoriness. In addition, the Seattle scientists believe that knowledge of the association of antigens important for the development of GVHD and the X and Y chromosomes in man might lead to the development of *in vitro* typing techniques to detect these antigens. Availability of such typing techniques will facilitate the selection of donor recipient pairs for marrow transplantation in aplastic anemia.

This study was reported in the April 1977 issue of *The Journal of Clinical Investigation* by Rainer Storb, Ross L. Prentice, and E. Donnall Thomas.

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News Feature

TEENS ARE FOUND TO BE MORE SEXUALLY ACTIVE

Between 1971 and 1976, sexual activity among unmarried U.S. women aged 15-19 increased by 30 percent. Over half (55 percent) of these teenagers have had sexual intercourse by age 19. At the same time there has been a dramatic increase in teenage use of oral contraceptives and the IUD, and more regular use of all methods of contraception. Nevertheless, few teenagers begin use of contraception at the same time they initiate intercourse--and many wait until they have experienced pregnancy.

These are the findings of Dr. Melvin Zelnick and Dr. John F. Kantner of the Department of Population Dynamics of the Johns Hopkins University. The 1971 and 1976 studies were supported by a grant from the NIH's National Institute of Child Health and Human Development.

In the spring and summer of 1971, a study was conducted by the investigators with a national probability sample of nearly 4,000 women aged 15-19 living in households and in college dormitories in the continental U.S. The sampled portion included women of all marital statuses and races. In 1976, a similar study was conducted of a national probability sample of 1,900 teenaged women residing in the U.S.

In the 1971 study, questions which were presumed to be more "sensitive" were included in a self-administered questionnaire. In 1976 all questions were asked by an interviewer, but using a randomized response technique which permits the respondent to

(more)

screen their sensitive answers from the interviewer but not from the final data.

In addition to the surprising increase in the prevalence of sexual activity by teenage women in the U.S., there were several other important findings, detailed as follows:

* 41 percent of the respondents in 1976 knew the time of greatest risk of pregnancy in the menstrual cycle--up three percent from 1971, but a poor showing stressing the need for sex education in this country.

* Most initial and subsequent sexual encounters took place in the home of the girl or her male partner. The older the girl the more likely it was to be the partner's home. For other locations, whites favored automobiles, blacks favored motels.

* Along with the increase in sexual activity, there has been an increase in the number of partners with whom teenage women have been involved. This may be a factor of earlier sexual initiation and more postponement of marriage.

* At first intercourse, male partners were usually teenagers. The most recent partner tended to be out of his teens.

* The age of first intercourse declined from 16.5 to 16.2 years, and nearly two-fifths of the respondents first experienced intercourse during the summer.

* About 64 percent of the respondents had used contraception at the time of last intercourse in 1976, as compared to 45 percent in 1971. This represents a dramatic increase.

* The time between first intercourse and first use of con-

(more)

traception has not narrowed significantly since 1971. Those who delayed were more likely to have had a pregnancy.

* Many more women used the pill and the IUD in 1976 than in 1971. At the same time, there has been a substantial decrease in the use of the condom, douche, and withdrawal, which were most prominent in 1971. Only among the very young teenagers were these methods of choice.

* Oral contraception was more popular among blacks than whites at every age, but it was for both groups the most popular method. About half of those using the pill received their prescription from a clinic rather than a private physician.

* In the 1971 study, sexually experienced teenage women had intercourse infrequently (during the month preceding the survey, two in five abstained); teenagers in 1976 appeared even more abstemious. This finding may have important implications for appropriate contraception for teenagers, whose contraceptive needs may vary greatly from those of stable couples with more frequent and regular sexual encounters.

These findings were published in the March/April 1977 issue of *Family Planning Perspectives.*

#

News Feature

CELLULAR IMMUNE RESPONSE IS SEEN IN THYROID CANCER PATIENTS

Boston investigators, in work supported partially by NIH's National Institute of Allergy and Infectious Diseases, have reported that medullary thyroid cancer patients and some of their relatives at risk for the disease exhibit a specific immune response to thyroid-tumor antigens. These findings support other evidence for an immune response to human, tumor-associated antigens and raise additional questions about the relationship between tumor immunity and cancer.

How the body protects itself against the development of cancer is poorly understood, but some scientists believe that the cellular immune response, mediated by lymphocytes, play a key role. This response is thought to act as a type of immune surveillance system triggered by the presence of tumor-associated antigens, specific proteins located on the surface of certain cancer cells. In the presence of these antigens, the lymphocytes, functioning as specific immune defense cells, increase in number and produce intermediary substances that fight off cancer cells. Two laboratory measurements of this response are lymphocyte proliferation and the production of migration inhibitory factor (MIF), a substance that inhibits the migration of guinea pig macrophages in a capillary tube.

Cellular immunity has been observed in patients with breast and other types of cancer, and, in some cases, in their relatives and in household contacts. No one knows why certain people develop

this response and others do not. Scientists feel that a better understanding of cellular immunity may lead to improved methods of cancer detection and treatment, including immunotherapy.

In the presently reported study, the investigators selected a family with a history of medullary thyroid cancer (MTC), a genetic disease affecting nearly 50 percent of family members. Although the course of the disease is frequently unpredictable, it is sometimes detectable in the early stages. High levels of calcitonin in the blood, a hormone produced by the thyroid gland, usually indicate a precancerous condition. Although the role of the cellular immune response in MTC is unclear, the high frequency of the disease in affected families makes it a good model for studying the clinical significance of the response.

After examining thyroid tissue and measuring calcitonin levels, the researchers divided the 56 family members into four groups according to their clinical status with MTC. Group I included 18 patients with the disease; Group II - seven patients with C-cell hyperplasia, an abnormal increase of thyroid cells thought to be precancerous; Group III - 12 members without disease symptoms but genetically at risk for MTC; and Group IV - nine members who had no symptoms and were not considered at risk.

Then, the scientists tested each person's response to normal and to thyroid-tumor antigens. The lymphocyte proliferation response and the production of MIF were used as indicators of a speci-

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fic cellular immune response. In addition, twenty-five normal people were used as controls and five patients with Graves' disease (hyperthyroidism) were included to verify the specificity of the response.

In agreement with previous studies, the researchers found that lymphocytes from 12 of 18 patients with MTC exhibited a specific cellular immune response to thyroid-tumor antigens. In addition, four of the seven patients with C-cell disease exhibited a similar response.

Of special interest, according to the researchers, is the fact that six of the 12 normal family members at risk for MTC also responded specifically to the tumor antigens. In contrast, cellular immunity was observed in only two of the 25 normal subjects and in only two of the nine normal family members not at risk.

Although the presence of a cellular immune response in healthy family members at risk is inexplicable, the researchers suggest that laboratory measurements of cellular immunity may be detecting early C-cell disease in these people. They add, however, that further studies are needed to prove this hypothesis.

More importantly, these findings raise interesting and conflicting thoughts about the role of immunity in the development of cancer. It is not known whether the development of a cellular immune response offers protection against MTC or causes its spread. If patients with MTC possess cellular immunity to tumor antigen, why did the disease develop and why can't they rid themselves of

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it? One explanation, proposed by the investigators, is that the presence of inhibiting blocking factors produced by the tumors prevents the cellular immune response from being protective in these people.

To further clarify the role of cellular immunity in family members at risk, the researchers suggest a clinical follow-up of these people to determine if any of them develop C-cell disease or MTC. In addition, they also recommend following patients with MTC and those with C-cell disease to see whether those with a cellular immune response differ in their long-term survival from those without the response.

The report of this research by Ross E. Rocklin, Robert Gagel, Zoila Feldman, and Armen Tashjian from the departments of Medicine and Pharmacology, Harvard Medical School, the departments of Medicine, Robert B. Brigham Hospital and Tufts New England Medical Center, and the Laboratory of Pharmacology, Harvard School of Dental Medicine, appeared in the April 14, 1977 issue of *The New England Journal of Medicine*.

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NEWS & FEATURES From NIH July 1977

News Feature

IOWA SCIENTISTS STUDY ROLE OF SALT IN BLOOD PRESSURE

Physicians at the University of Iowa College of Medicine and Hospitals, Iowa City, report that some individuals may be very sensitive to the deleterious effects of salt on blood pressure, while others may be resistant.

The report is the result of studies on young adults at the University of Iowa Clinical Research Center, one of 83 such units located at medical institutions throughout the United States and funded by NIH's Division of Research Resources. This clinical research unit within the larger hospital provides specialized patient-centered research facilities to the entire University of Iowa College of Medicine staff.

The Iowa studies involved two groups of young adults--one with normal blood pressures and another with slight or early hypertension. For 10 to 30 days, the six individuals in each group ate diets with either high or low amounts of salt.

Because the individuals were studied in the Clinical Research Center, research dietitians were able to vary the salt intake and keep all other ingredients in their diets constant. In order to insure the safety and accuracy of the diets, the blood pressures, body weights, kidney and hormonal functions, and general physical condition of the patients were assessed daily by research nurses and by a physician who specializes in the treatment of hypertension.

As the research neared its conclusion, detailed studies of circulatory control were performed on the patients by cardiologists

(more)

SALT (CONT'D)

from the University of Iowa Cardiovascular Research and Training Center. These studies, which were conducted through funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health, helped determine the effect of salt on the blood pressures and blood vessels.

According to Dr. Allyn L. Mark, Program Director for the University of Iowa Clinical Research Center, and Dr. Francois Abboud, Director of the Cardiovascular Center, the surprising and important finding of the study was a distinct difference in the effects of a high salt diet on the patients with normal blood pressures as compared to those with slightly elevated blood pressures.

"Excessive salt raised blood pressure and constricted blood vessels in patients with slight hypertension, but it relaxed the blood vessels and failed to elevate blood pressures in the individuals with normal blood pressure," Dr. Mark says. "This indicates that some individuals may be very sensitive to the deleterious effects of salt on blood pressure, while others seem to be resistant.

"The research raises the intriguing possibility that sensitivity to salt may be a factor in predisposition to hypertension. This finding may have important implications in the prevention and treatment of hypertension."

Dr. Mark reports that additional research studies evaluating the relationship between salt and hypertension are in progress at the University of Iowa Clinical Research Center and Cardiovascular Center.

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News Feature

NIGMS ANNOUNCES GRANTS PROGRAM IN TRAUMA AND BURN RESEARCH

A special grants program to encourage new investigators in the field of trauma and burn research has been announced by NIH's National Institute of General Medical Sciences.

To be eligible, applicants must have an M.D. degree at the time of the award and present evidence of prior research training.

A major purpose of the awards is to facilitate the transition from a research training status to that of a productive investigator by providing initial support for independent research during the transition period.

In this way, it is expected that the new program will help increase the number of talented physicians engaging in research on urgent and complex problems associated with seriously injured patients, including burn victims.

The proposed research should be directed to the discovery of better ways to prevent death from injury, mitigate pain, speed the recovery of patients, and lessen the extent of disabilities.

Fundamental approaches to a better understanding of the body's total response to trauma and burns are sought, as are studies on such problems as sequential organ failures, nutritional requirements, wound healing, infections, and rehabilitation.

The initial receipt date for applications is November 1 of this year. Subsequent receipt dates, in 1978, are March 1, July 1, and November 1.

Copies of a program announcement which sets forth guidelines

(more)

PROGRAM (CONT'D)

for submitting the special grant applications may be obtained from the NIGMS Trauma-Burn Research Program Room 955, Westwood Building, Bethesda, Maryland 20014. The telephone number for the Program office is (area code 301) 496-7047.

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SIDS--The sudden infant death syndrome (SIDS) is the leading cause of death in infants after the first month of life, claiming the lives of three infants for every thousand live births, according to the National Institutes of Health.

NEWS & FEATURES From NIH

July 1977

News Feature

NCI PUBLISHES HISTORY OF CANCER OVER 5,000 YEARS

A history of cancer research over the past 5,000 years, entitled *Contrary to Nature,* has been published by NIH's National Cancer Institute.

The book was written by a noted cancer scientist, Dr. Michael B. Shimkin, Professor of Community Medicine and Oncology at the University of California, San Diego, and former president of the American Association for Cancer Research.

In the prologue of the book, which is dedicated to the eventual prevention and cure of cancer, Dr. Shimkin offers the hopeful prediction, "Today cancer is among the diseases aptly called by the ancients as 'tumors contrary to nature'. Tomorrow it will be among the horrors of the past. Its conquest will be by man's intellect, using a disciplined yet unbridled method of imagining and thinking called scientific research."

The chronicle points out that cancer was described and found in mummies dating back to the Egyption Third to Fifth Dynasties, some 5,000 years ago, and "it is more than probable that cancer afflicted animals long before man appeared on earth."

The history traces the whole of man's efforts to study and cope with cancer throughout the ages, with numerous illustrations from contemporary publications.

The commentary is divided into historical periods from those preceding written history, through the age of Galen and Hippocrates (500 B.C. to A.D. 500)--when cancer was named by the Greeks and

(more)

ascribed to "an excess of black bile," one of the "four humors" of the body--to the development of modern methods of treatment and a growing understanding of the causes of cancer.

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MIDDLE EAR--Inflammation of the middle ear space can lead to conductive hearing loss by blocking sound which must pass through the middle ear to the inner ear where it is processed and sent to the brain, according to the National Institutes of Health.

News Feature

PROMISING RESULTS ARE NOTED IN USE OF TWO MOUTHRINSES

Investigators at NIH's National Institute of Dental Research, report promising results with two substances used as mouthrinses to prevent tooth decay in animals. One is a fluoride variant of the experimental antibiotic, alexidine, and the other, stannous fluoride, an ingredient of several dentifrices.

Dr. Roald Shern and others in the National Caries Program noted that alexidine has already proved fairly successful as a human mouthwash. They reasoned that a fluoride salt of alexidine might prove even more effective. Therefore they infected several groups of rats with decay-causing bacteria and fed them a sugar-rich diet. During the 56 days of the experiment, food and water were withheld only for half an hour after each mouthrinse which occurred once a day for five days each week. The compounds compared in this way were sodium fluoride, alexidine dihydrochloride, a combination of amine fluorides, and alexidine dihydrofluoride, each dissolved in a basic solvent. As a control, that solvent (12 percent ethyl alcohol and water) was also tested.

As predicted, the alexidine dihydrofluoride gave the greatest protection against tooth decay. It was especially effective for protecting the smooth side surfaces of teeth. The control animals developed an average of nearly 45 decayed areas on smooth surfaces and a total of 74 on all surfaces. In contrast, the animals protected with alexidine dihydrofluoride had 15.5 and nearly 45 decayed areas respectively.

(more)

MOUTHRINSES (CONT'D)

In another series of animal tests, Dr. Shern compared an experimental chemical (tiodonium chloride, not suitable for human use but known to reduce bacterial plaque) with stannous fluoride and with distilled water. Again the rats were infected with decay-causing bacteria and fed a sweet, powdered diet. Plaque was allowed to accumulate for a week and then stained and inspected before rinsing began.

The rinsing was done twice a day for seven days and thereafter the amount of plaque and the acid response to an application of a solution of mixed sugars was measured.

There was 71 percent less plaque in the SnF treated animals than in the placebo group and in addition the plaque from the fluoride treated animals had little acid producing capacity.

Dr. Shern commented that previous experiments have shown that when animal teeth are clean, low concentrations of stannous fluoride (500 parts per million F-) maintain freedom from plaque. This experiment shows that a 2 percent solution (5,000 parts per million F-) will remove existing plaque in a relatively short time. Therefore if the human response is similar to the animals, it might be possible to bring plaque quickly under control with a concentrated rinse, and then to maintain control with a dilute mouthwash. Such a preventive treatment would be safe and economical.

The chief problem with stannous fluoride is a tendency to stain teeth. Alexidine also stains superficially, but so far alexidine is available only for experimental use. Another unsolved problem

(more)

MOUTHRINSES (CONT'D)

common to all preventive agents is how to deliver them down into the crevices and pockets around teeth.

This research was reported at the annual meeting in Las Vegas, Nevada, June 1977, of the American Association for Dental Research by Roald J. Shern, D.D.S., Suzanne M. Amsbaugh, B.S., George R. Reynolds, Jr., B.S., and Kathleen M. Couet, B.S.

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GOUT--Victims of gout can now be taken care of with reasonable comfort and can be assured that their disorder, if diagnosed early and treated properly, will not cripple them, according to the National Institutes of Health.

News Feature

REPORT IS AVAILABLE ABOUT PROFLAVINE TESTS

Availability of a report on animal tests of proflavine for cancer-causing activity was announced by NIH's National Cancer Institute in the *Federal Register* for July 12, 1977.

Proflavine (3,6-diaminoacridine) is a synthetic acridine dye which early in this century was found to have bacteriostatic and bacteriocidal properties when administered topically. During World War II, it was widely used as a wound antiseptic. With the advent of more specific and less toxic antibiotics, its clinical importance declined until it was reintroduced recently in combination with ultraviolet light for the treatment of psoriasis and type-II herpes virus infection.

The compound was fed to rats and mice for approximately two years. According to a summary of the report included in the announcement, "The observed incidence of hepatocellular carcinoma in female mice was 4/50 (eight percent) in the control group, 20/49 (41 percent) in the low-dose group, and 22/50 (44 percent) in the high-dose group. In male mice, the observed incidence of hepatocellular carcinoma was 20/49 (41 percent) in the control group, 28/49 (57 percent) in the low-dose group, and 30/50 (60 percent) in the high-dose group.

"Five malignant neoplasms of the intestinal tract, consisting of three leiomyosarcomas of the small intestine, a sarcoma near the colon area, and an adenocarcinoma of the small intestine were observed in five of the high-dose male rats. None were observed

(more)

PROFLAVINE (CONT'D)

in other treatment or control groups."

However, because of an unusually high tumor incidence in control animals, results are considered inconclusive by the Institute.

The tests were part of the Institute's Carcinogenesis Bioassay Program. Copies of the report are available from the NCI Office of Cancer Communications, Bethesda, Maryland 20014.

#

ENDOCRINOLOGY--Endocrinology, the study of the internal glandular secretions of the body, is an immense biomedical field which directly pertains to important life functions, such as growth, metabolism, and reproduction, according to the National Institutes of Health.

Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

Ms. Joyce Flaherty
National Institutes of Health
Building 31, Room 2B-10
Bethesda, MD 20014

Dear Ms. Flaherty:

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September 1977

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September 1977

PANEL STUDIES BREAST CANCER SCREENING

After an extensive review of data collected within a nationwide project to demonstrate breast cancer screening, an NIH National Cancer Institute sponsored Working Group recommended on September 15 that the project be continued as a demonstration program.

Led by their chairman, Dr. Oliver H. Beahrs of the Mayo Clinic, Working Group members reported eight additional conclusions and recommendations bearing on the future of the project. The report was presented to a panel of lay people and leading scientists and clinicians convened by the National Institutes of Health and NCI to attempt to reach a consensus on modalities for breast cancer screening.

The Beahrs Group recommended that mammography be continued in the Breast Cancer Detection Demonstration Project (BCDDP), co-sponsored by NCI and the American Cancer Society, as a routine screening modality for all women 50 years of age and older.

The recommendation added that mammography should be used to screen women ages 40 to 49 only when the women have a personal history of breast cancer or a history of breast cancer in first degree relatives (mother or sisters), and women ages 35 to 39 only when they have a personal history of breast cancer.

The Group's recommendations for continued use of mammography are identical with guidelines now in effect within the BCDDP for women 40 years of age and older. For women 35 to 39 years of age,

(more)

SCREENING (CONT'D)

current BCDDP guidelines also allow use of mammography to screen women who have a history of breast cancer in first degree relatives, while the Beahrs group recommends that use of mammography in this age group be restricted to those who have a personal history of breast cancer.

Thermography, another modality used for screening in the BCDDP, which records heat patterns on the surface of the breast, "does not appear to be suitable as a substitute for mammography in routine screening in BCDDP," the Group's report states.

Randomized controlled studies in breast cancer screening should be started on questions not answerable with data available from the BCDDP, the Beahrs Group recommended.

These questions include the magnitude of benefit and the net benefit (benefit-less-risk) in use of mammography, benefit in screening at ages 40 to 49, and the effect of increasing the interval between screenings.

All nine conclusions and recommendations of the Beahrs Group follow:

1) That the BCDDP be continued as a demonstration program for the remainder of the planned five annual screenings.

2) That physical examinations be continued in BCDDP as a routine screening modality for all ages.

3) That mammography (or Xeroradiography) be continued in BCDDP as a routine screening modality for:

a) all women 50 years of age and older.

(more)

SCREENING (CONT'D)

b) women at ages 40 to 49 only when they have a personal history of breast cancer or a history of breast cancer in first degree relatives (mother or sisters).

c) women at ages 35-39 only when they have a personal history of breast cancer.

4) That thermography be discontinued as a routine procedure in the BCDDP for all ages.

5) That a concurrent review of pathology for minimal cancers be activated; also a concurrent review of mammography and monitoring of quality of the physical examination. Existing monitoring and control measures for radiation dosage should be maintained.

6) That the informed consent form provide women having routine mammography a reasonable basis for weighing radiogenic risks against known benefits or against benefits not established but which BCDDP experience suggests might result from including mammography.

7) That follow-up after the planned five annual screenings be restricted to breast cancers detected. Follow-up should be for a minimum period of 10 years after diagnosis: the minimal cancers form a unique group of cases for the study of the natural history of breast cancer.

8) That randomized controlled studies in breast cancer screening be started on questions not answerable from BCDDP. These include magnitude of benefit and net benefit-risk in use of mammography, benefit in screening at ages 40-49, effect of increasing the interval between screening.

(more)

SCREENING (CONT'D)

9) That the Working Group continue its review of various issues related to BCDDP."

The Beahrs Working Group was established in January, 1977 by NCI's Division of Cancer Control and Rehabilitation. The Group was asked to review the current BCDDP to determine, first, what scientific information is now available from the BCDDP, which was established as a demonstration project rather than as a controlled, clinical trial. Second, the Group was to determine whether the projects provide any suggestive evidence that could guide the development of a clinical trial. Third, and if appropriate, the Group would develop a plan for such a clinical trial and consider the use of the BCDDP to conduct such a trial.

Copies of the Beahrs report are available from the Office of Cancer Communications, NCI, Bethesda, Maryland 20014.

(N I H Photo #1604)

#

SCIENTISTS EXPLORE ROLE OF GENE-ENVIRONMENT INTERACTION

A key that may someday unlock one of the most mysterious areas of human biology--the role of gene-environment interaction in birth defects--has been discovered by scientists at NIH's National Institute of Child Health and Human Development (NICHD).

From this and future discoveries, it may someday be possible to detail how a specific gene and a specific environmental pollutant act together at the cellular level to cause disease, disability, or death. Elucidating this process would be invaluable in explaining individual susceptibility to birth defects, degenerative diseases, poisoning by environmental chemicals, and environmentally-caused types of cancer.

The key to this understanding may be found in a genetic system discovered through research headed by Dr. Daniel Nebert, chief of the NICHD Developmental Pharmacology Branch. He and his co-investigators have found that in the adult animal, this system protects against certain environmental, drug and foreign substance poisoning, but *in utero*, this same system may render the developing fetus susceptible to birth defects.

The genetic system--called the "*a*romatic *h*ydrocarbon responsiveness locus"--is present in the cells of many animals, including man. It consists of one gene or a small number of genes, which control the body's capacity to rid itself of numerous toxic substances.

Among these are hydrocarbons in cigarette smoke, charcoal-

broiled foods, and automobile exhaust fumes. Other chemicals whose fate is determined by the *Ah* locus include fat-soluble compounds used as drugs, insecticides, and raw materials for industry.

If allowed to accumulate in tissue, many of these substances are poisonous and may cause cancer, birth defects, or mutations.

When one of these toxicants enters a cell, the *Ah* locus in the cell's nucleus is activated in some as yet unknown manner. Activation of the *Ah* locus boosts the activity of a series of enzymes called monooxygenases. These enzymes modify the original toxic chemical into a new substance which can be attacked and further broken down by another set of enzymes. The final product is a harmless substance which can be excreted from the cell and from the body.

Individual humans and various strains of laboratory mice differ in their enzymatic response to hydrocarbons. In mice having a "responsive" form of the gene(s) at the *Ah* locus, hydrocarbon exposure prompts dramatic rise in monooxygenase enzyme activity.

In other mice, called "nonresponsive" the increase does not occur at all in the liver and is small in other tissues.

Through a series of crosses between "responsive" and "nonresponsive" mice, NICHD scientists studied pregnancies in which fetuses of both genetic types were present in the same womb. In this situation the scientists observed that when the pregnant mouse was exposed to a polycyclic hydrocarbon, fetuses with the

(more)

INTERACTION (CONT'D)

responsive gene(s) at the *Ah* locus suffered massive deformation.

About 75 percent of the "responsive" fetuses were deformed or killed, and virtually all of the survivors were growth retarded. Specific malformations included cleft palate, club foot, absence of an eye, nose and jaw underdevelopment, kidney or liver abnormalities, and heart protrusion outside of the body cavity.

In contrast, the "nonresponsive" mice from the same litter suffered fewer malformations, only a slight growth inhibition, and a much lower death rate.

This study proves that genetic factors within fetal tissues can determine fetal susceptibility to birth defects when the baby in the womb is exposed to chemicals by way of the mother.

Results also suggest a possible explanation for the low birth weight of human infants whose mothers smoke cigarettes during pregnancy. It seems likely that this form of intrauterine growth retardation may be caused by hydrocarbons "triggering" the *Ah* locus.

Although demonstrated to be of potential harm to a fetus, the responsive form of the gene(s) at the *Ah* locus can be of considerable survival value for an adult animal receiving hydrocarbons in its food. This trait enables the animal to dispose of the hydrocarbons more efficiently, before build-up to toxic levels can occur.

This apparent contradiction can be explained partially by earlier studies showing that the first products of monooxygenase

(more)

INTERACTION (CONT'D)

activity are highly reactive compounds. They can damage the cell's genetic material if not detoxified immediately.

Apparently, fetuses genetically responsive to hydrocarbons may form these dangerous intermediates in sufficent quantity to cause irreparable damage to their tissues. The nonresponsive fetuses may be protected by their inefficiency in coping with hydrocarbons.

Laboratories around the world are now attempting to apply *Ah* locus information to the prevention of human disease. A search is underway to identify human groups or individuals whose *Ah* responsiveness places them at risk for diseases caused by environmental chemicals.

NICHD researchers are collaborating with National Eye Institute investigators to determine whether the *Ah* locus plays a role in causing cataracts to form in response to certain drugs and in causing retinitis pigmentosa, a degenerative disease of the eye.

Current NICHD studies aim at a more detailed understanding of the monooxygenase enzymes and the genetic control mechanisms enabling the *Ah* locus to respond to hydrocarbons.

Dr. Nebert will present these findings in detail at the Ross Symposium to be held November 21, 1977, at La Sapinère, Val-David, Quebec, Canada.

#

CHOCOLATE MIGHT NOT BE GOOD FOR NURSING MOTHERS

The folkbelief that chocolate causes adverse affects in nursing infants has some basis in fact, as reported in recent studies by grantees of NIH's National Institute of General Medical Sciences.

With the resurgence of breast-feeding in the mid 1970's, increased attention has been focused on the transmission of hazardous chemicals from foods into human milk. This increased interest has also brought under closer scrutiny the basis of many commonly held myths about breast feeding.

It is a common claim in the folklore of breast feeding that chocolate eaten by nursing mothers has adverse effects on their infants. Diarrhea, constipation, and eczema in breast-fed infants are some of the effects attributed to chocolate. Until now, no mechanism explaining the adverse effects of chocolate in nursing infants has been reported. Theobromine, a caffeine-like substance, is present in all chocolate products. As with other methylxanthines, theobromine can cause central nervous system stimulation, diuresis, stimulation of cardiac muscle, and relaxation of smooth muscle.

Other studies have been conducted with caffeine and theophylline, two other methylxanthines found in everyday foods--caffeine primarily in coffee, tea, and cola; and theophylline in tea. These studies in newborn infants demonstrated the transfer of caffeine and theophylline into human milk. But more significantly, these studies revealed extremely slow drug elimination by the

(more)

infants. Thus it is possible that theobromine in nursing infants may have a similarly slow rate of elimination.

Consequently, if nursing mothers frequently ate chocolate, their breast-fed infants could accumulate substantial amounts of theobromine through the milk. This accumulation could cause some of the purported effects of chocolate consumption.

Research conducted by Beth H. Resman, Pharm. D., H. Peter Blumenthal, M.D., and William J. Juso, Ph.D., at the State University of New York at Buffalo investigated the absorption and distribution of theobromine from chocolate. Six nursing mothers, aged 21-36, who had been breast feeding their infants from 3-37 weeks, participated in this study. The participants were asked not to consume any tea, coffee, cola drinks, or chocolate for 24 hours prior to the study, and to observe an overnight fast. After blood, milk, and saliva samples were taken, the mothers ate 113 gm (4 ounces) of Hershey's milk chocolate. The amount of theobromine contained in four ounces of Hershey's milk chocolate is similar to the amount (240 mg) used as a single pharmacologic dose. Blood, milk, and saliva samples were then collected at regular intervals up to 14 hours.

Peak theobromine concentrations of 3.7 to 8.2 mg/l were found in all fluids at 2 to 3 hours after ingestion of the chocolate. The concentration of theobromine in plasma, milk, and saliva generally declined in parallel with elimination half-life of theobromine averaging 7.1 ± 2.1 hours. No change in the relative theobromine concentrations in milk or plasma occurred upon breast

(more)

CHOCOLATE (CONT'D)

feeding, and essentially identical concentrations of theobromine were found in the milk at the beginning and end of nursing.

Based on averaged data, if a nursing mother ate a four-ounce chocolate bar every six hours and her infant ingested a liter of milk daily, nursing when the theobromine concentration was at a peak, the infant could be exposed to about 10 mg of theobromine, or approximately 1 to 2 mg/kg/day. This dosage would probably not be pharmacologically significant in most infants, but could produce effects in some sensitive individuals.

This research was reported in the September 1977 issue of *The Journal of Pediatrics*.

#

This report was prepared by Sheila Pohl, NIH.

PARENTS, NOT GENES, MAY CAUSE OBESITY

Until recently, a plump baby was the parents' assurance that their infant was healthy and thriving. Many pediatricians reinforced this association, believing that fat babies were healthier babies.

But now, in the face of new research findings, pediatricians are beginning to urge parents to control the weight of their offspring.

Scientists have found that rather than being a sign of good health, infant or childhood obesity can be the harbinger of later medical problems. Long-term studies have shown that childhood obesity is closely related to obesity, hypertension, and diabetes mellitus in adulthood. Thirty-six percent of those infants whose weight exceeds the 90th percentile during the first six months of life become overweight or obese adults, and at least 80 percent of all diabetes occurs in the obese or the once obese.

These and other findings were discussed at a recent NIH workshop on obesity and diabetes sponsored by the National Institute of Child Health and Human Development (NICHD).

Because obesity is often observed to "run in families", many persons, including some physicians, have assumed that there is a genetic link. But now it is thought that inherited obesity is uncommon.

Although it is true that the children of obese parents become obese three times more often than children whose parents are of

(more)

normal weight, many times there is no genetic reason for this to be the case, according to workshop reports.

Rather, recent studies with adopted obese children have found that it is acquired patterns of eating such as preferences for certain types of food, rate of food consumption, and meal timing that are usually passed on from generation to generation, not genes for obesity.

Researchers say that other early family influences contribute to the syndrome of parent-child obesity. These include exercise habits, family socioeconomic status, and behavioral traits such as a family's practice of rewarding good behavior with sweets or increasing food consumption in response to stress or worry.

Breaking this cycle of familial obesity is usually a difficult task for a physician. Often, in order to treat the overweight infant or child, the parents must be persuaded to modify their own eating and exercise habits. This usually includes teaching the family the basics of good nutrition and more healthful eating habits.

One type of childhood obesity discussed at the workshop that may have a genetic basis is characterized by hyperplastic (increased number) and hypertrophic (enlarged) adipocytes, the body's fat storage cells. Children suffering this form of obesity are massively overweight and remain that way for life.

This type of obesity is relatively rare; more commonly, obese children are found to have populations of hypertrophic adipocytes

(more)

that are no more numerous than those of their lean companions, it was reported.

Even though massive juvenile obesity appears to be genetically determined, the mechanics of transmittal are not known. Workshop participants agreed that additional research is needed on the genetics of obesity. Less is known about the genetics of human obesity than of any other major disorder, they say.

Also identified at the workshop as in need of intensive study are the development of taste preferences and the mechanism of imprinting the hypothalamus, that portion of the brain that has been identified as the appetite and thirst control center.

Recent research has shown that human infants develop strikingly different taste preferences within the first week of life. Such predilections may be determined genetically or by the intrauterine environment. Because taste guides the patterns of ingestion for life, scientists say understanding the genetics, biochemistry, and psychology of the development of taste would have important implications in the management of obesity.

Likewise, understanding the drive to overeat would have important clinical implications. That part of the brain (the hypothalamus) which regulates sensations of hunger and satiety has been identified, but the process which triggers the hypothalamus to signal "enough" is not understood. The process may depend on genetic inheritance, the intrauterine nutritional environment, or

(more)

on the timing and quality of nutrient intake during the first weeks after birth. How (or if) this process is affected by prematurity, overfeeding, intrauterine starvation, or ingestion of drugs or alcohol by the mother during her pregnancy should be studied in order to better understand the problems of overeating and obesity in childhood, NICHD scientists say.

#

NCI PUBLISHES REPORT ON PATIENT SURVIVAL

Survival rates for six of the ten most common forms of cancer in the United States have improved gradually since the early 1960's, according to a newly published report by NIH's National Cancer Institute (NCI).

Increased survival was noted for patients with cancers of the bladder, breast, colon (large intestine), prostate, rectum, and uterine corpus (the body of the uterus, excluding the cervix). Rates have remained unchanged for cancers of the cervix, lung, pancreas, and stomach.

Cancer Patient Survival, Report No. 5 is the latest in a series of comprehensive reports on the survival experience of cancer patients. The 315-page report provides data for the period 1950 through 1973, analyzed with respect to age, race, sex, primary site, cell type, extent of disease and treatment.

Editors of the report were Max H. Myers, Ph.D., Lillian M. Axtell, M.A., and Ardyce J. Asire, M.S., of the NCI End Results Section. Nine other NCI statisticians participated in the review of data for 39 forms of cancer. The scientists analyzed data for 453,467 patients whose initial diagnoses and subsequent treatment progress were reported to one of four registries: California Tumor Registry, Berkeley; Charity Hospital of Louisiana, New Orleans; Connecticut Tumor Registry, Hartford; and State University of Iowa Hospital, Iowa City.

For many of the 10 leading forms of cancer (as reported in

(more)

SURVIVAL (CONT'D)

the NCI Third National Cancer Survey of 1969-71), five-year relative survival rates have improved gradually since the early 1960's, although rates in general were higher for whites than for blacks. In the current study these 10 forms of the disease accounted for 63 percent of cancers in white patients and 65 percent in black patients.

The five-year relative survival rate for all types of cancer combined increased slightly from 39 percent for 1950-59, to 40 percent for 1960-66 and 41 percent for 1967-73. For blacks, the rates were 29 percent, 28 percent and 32 percent, respectively. Complete five-year followup is not yet available for cancer diagnosed in 1970 or later. The latest five-year rate therefore represents an extrapolation of available data to five years.

Relative survival is an adjustment of observed survival for deaths due to causes other than cancer. The rate is defined as the ratio of the observed survival rate for a group of patients to the expected survival rate of people in the general population similar in age, sex, race, and calendar year of observation.

The greatest improvements for white patients were for cancers of the bladder and prostate. Improvements among blacks occurred predominantly for cancers of the breast, prostate, bladder and rectum.

Where the percent of patients diagnosed with localized cancers remained unchanged, as with prostatic cancer among white men, increased survival may reflect improvements in treatment, the

(more)

SURVIVAL (CONT'D)

NCI scientists said.

Differences in survival between white and black patients were similar in this study to those in previous NCI reports and may reflect socioeconomic factors not yet identified in detail, they noted.

For two less common cancers, Hodgkin's disease and acute lymphocytic leukemia, the NCI analysis reflected the upswing in survival reported by some research centers.

Five-year survival for white patients with Hodgkin's disease in the most recent time period was 54 percent; the corresponding rate for patients diagnosed in 1950-54 was 30 percent.

For white patients with acute lymphocytic leukemia, one-year survival has improved steadily, from 10 percent in the early 1950's to 71 percent in the 1970's. Three-year survival increased from less than 1 percent to 16 percent in the same period. The greatest improvement occurred for children under 15, whose three-year survival rate was 34 percent in the latest time period. As with several of the less common cancers, the numbers were too small in blacks to compute similar comparisons.

Dr. Myers, who headed the statistical project, emphasized that the data in the report are "aggregate figures to provide overall impressions" of survival experience. "The rates," he said "do not apply to individual patients...." but provide an indication of average rates for a large population of patients.

Moreover, five-year survival is not the same as "cure" in

(more)

SURVIVAL (CONT'D)

these patients, he indicated. Some cancer patients may experience the disease again many years after its apparent absence, although they were freed of their initial disease following treatment.

In examining their data, the NCI editors noted that although the patient population in their study is limited to four registries and, "....it is difficult if not impossible to assess whether data contributed by these registries are a true reflection of cancer patient survival throughout the United States...the data presented in this report reflect a spectrum of types of patients and hospitals and there is no strong evidence of bias...."

Single copies of *Cancer Patient Survival, Report No. 5* are available free of charge from the Office of Cancer Communications, National Cancer Institute, Bethesda, Maryland 20014.

#

DOCTORS AID DIABETIC PATIENTS WHO NEED KIDNEY TRANSPLANTS

Researchers at the University of Minnesota Hospitals, using a specially-funded clinical research unit, have begun a five-year study to determine whether strictly regulating the diet and insulin medication of diabetic patients with kidney transplants can avoid the recurrence of blood vessel damage and kidney malfunction, a common problem among diabetics.

The investigation will be led by Dr. Jose Barbosa, Endocrinologist in the Department of Medicine, in close collaboration with Dr. John Najarian's organ transplant program.

Using the facilities of the medical center's General Clinical Research Center, the investigators are attempting to find out whether diabetic patients are predisposed to blood vessel and kidney damage or whether such damage can be avoided by strict physician management. The General Clinical Research Center is one of 83 such units located in medical centers throughout the United States and funded by the NIH's Division of Research Resources. This specialized clinical research unit within the larger hospital provides highly specialized research facilities to the entire staff of the University of Minnesota Hospitals.

According to Dr. Fred Goetz, program director for the Minnesota General Clinical Research Center, the study involves two groups of about 30 diabetic patients who have recently received kidney transplants. One group will have their blood sugar levels controlled through the generally accepted regimen of self-regu-

(more)

lation, while the other group will have their diets and insulin injections strictly controlled by physicians according to metabolic indicators.

The group under strict control will visit the University of Minnesota General Clinical Research Center about once a week to have their diets and insulin dosages adjusted according to the metabolic tests. Meanwhile, members of the control group will regulate their own diets and insulin injections. Both groups will spend about 10 days a year as inpatients in the Clinical Research Center at which time their kidney functions will be fully evaluated. During these periods of hospitalization, physicians will take a biopsy of the kidney to look for small vascular lesions which usually indicate the onset of damage due to diabetes. According to Dr. Goetz, such lesions usually appear on the kidney blood vessels of diabetic kidney recipients two to four years after a patient receives a new kidney. In diabetic patients who have their own kidneys, it is thought the lesions take 10 to 20 years to appear after the onset of diabetes.

Failure of function in the transplanted kidney has not occurred for as long as seven years following kidney transplantation.

"Recently transplanted patients should give us solid data on possible prevention of kidney damage in a study that takes place over a reasonable period of time," Dr. Goetz says. "With recently diagnosed diabetics, such a study might take up to 20

(more)

years before the lesions became evident.

"If the biopsies begin to show kidney vascular lesions present in the research group not under strict control, but no lesions in those patients who have been closely regulated, it would indicate that a diabetic is not predisposed to suffer vascular damage and eventually kidney failure. This evidence would suggest that such damage can be avoided if the diabetic is placed under the strict control of a physician rather than self regulation.

"Self regulation can, with relatively little effort, relieve all of the day-to-day symptoms of diabetes. Keeping blood sugar levels normal at all times is not necessary for this goal of diabetic treatment. But the blood vessel complications of diabetes which appear after many years are serious and there has been great uncertainty and some controversy about whether these complications might be prevented if day-to-day treatment were more precise.

"If there were more certainty on this relationship between high blood sugar and serious blood vessel complications, both patients and doctors all over the world would be much more motivated to work hard at diabetic treatment.

"This study should help clarify this situation for physicians and their diabetic patients."

Dr. Goetz emphasizes the importance of a unit like the General Clinical Research Center in the long term study with its sophisticated laboratories, diet kitchen, and personnel trained

(more)

AID (CONT'D)

to provide quality health care while at the same time carrying out meticulous research protocols.

"During the outpatient visits of those under strict control, we must get an accurate survey of blood sugar levels for each person in order to maintain a careful metabolic balance," Dr. Goetz says. "We also will carefully study the functioning of the kidney to check for any possible damage. Such studies, along with carefully calculated insulin dosages and diet regimens prescribed for each patient on strict control, make it imperative that a facility like the Clinical Research Center be available for this project."

Dr. Fred Goetz, principal investigator at the University of Minnesota General Clinical Research Center, checks a computer printout showing the results of laboratory tests on diabetic patients undergoing treatment on the special research unit. The sophisticated laboratory equipment is an example of the facilities supported by a grant from the National Institutes of Health's Division of Research Resources, which funds the 83 General Clinical Research Centers throughout the country. (N I H Photo # 1605)

#

NIH TEAM DESIGNS MECHANICAL SECTOR SCANNING SYSTEM

An NIH research team has developed an inexpensive ultrasonic real-time scanner for obtaining a cross-section view of the upper abdomen.

The researchers--Dr. Thomas H. Shawker, William H. Schuette, and Willard Whitehouse of the Clinical Center and Division of Research Services--designed the mechanical sector scanning system which permits simultaneous, continuous viewing of the abdomen.

Ultrasonic scanners operate on the same principle as the sound-echo system of bats which enables them to dodge obstructions while in flight. Bats send out a high-pitched sound that generates a series of echoes when striking an object.

Similarly, the ultrasonic scanner's pulsed sound signals send back echoes from the various tissue boundaries in the body.

The scanner receives and converts the echoes to electronic signals which are seen on the TV screen as a black and white cross-sectional image of the body.

Unlike conventional static ultrasonic B-scanners, real-time scanners give a continuous "fluoroscopic" image.

Although real-time scanners have been used for cardiac and obstetrical diagnosis, the investigators designed this scanner to be of maximum value for abdominal study.

The scanner uses a single element ultrasonic transducer which mechanically rotates through a ± 25 degree angle. A counter

(more)

SCANNING SYSTEM (CONT'D)

balancing rotation of the motor and transducer reduces mechanical vibration to a minimum.

A unique photoelectric feedback control permits a linear scan to be taken.

The unit is inexpensive and can be integrated as an "add-on" to commercially available static B-scanners. Transducers of different diameters and frequency can be interchanged, and the unit is electronically synchronized to a TV system for video recording.

The investigators have examined over 100 patients with the scanner and developed an examination technique for a rapid evaluation of the abdomen.

The unit is easily positioned on the skin, even-angled underneath the rib cage, and allows continuous viewing as the scanner is moved freely over the patient's body.

The resolution is sufficient to visualize the major arteries, veins, and upper viscera with normal physiological activity.

Although the group focused on normal patients for their initial study, the scanner is proving useful for detecting abdominal disease.

The pancreas, liver, and kidneys can be scanned for tumors, major arteries and veins examined for abnormalities, ascites detected, and the gall bladder checked for the presence of stones.

The research group is continuing studies on other applications of the scanner.

#

NCI TRIES VITAMIN E WITH ADRIAMYCIN IN MICE

Vitamin E lessens the harmful effects of the widely-used anticancer drug Adriamycin on heart muscle in a strain of laboratory mice, according to scientists at NIH's National Cancer Institute.

The vitamin protected normal tissue without diminishing the drug's activity against cancer in the animals. Dr. William McGuire reported these findings May 19 at the 68th annual meeting of the American Association for Cancer Research in Denver, Colo. Other NCI scientists participating in the study were Dr. Robert C. Young, Karen Grotzinger, and Dr. Charles E. Myers.

One of the most active anticancer drugs known, Adriamycin--a commercially available antibiotic--is active against at least 10 forms of cancer in man.

Unfortunately, a side-effect of the drug is deterioration of the heart muscle that may lead to congestive heart failure. This side-effect has limited the total dose of Adriamycin that any patient can receive to 550 mg per square meter of body surface.

The quinone group of the Adriamycin molecule has been suspected of being responsible for damage to cardiac tissue.

Quinones are known to interfere with the generation of energy in mitochondria and other cell components by producing unstable molecules called "free radicals".

These free radicals set off in the cells a chain of chemical

(more)

VITAMIN E (CONT'D)

reactions, one of which may be damage to the cell's membrane, resulting in cell destruction.

A chemical called malondialdehyde is produced by the interaction of free radicals and lipids in the membrane.

Examination of heart tissue from mice treated with toxic doses of Adriamycin revealed high levels of malondialdehyde, according to Dr. McGuire, indicating the possibility that free radicals were being produced. Malondialdehyde could not be detected in heart tissue of normal mice.

Because vitamin E reacts with free radicals, preventing their reaction with other compounds, the NCI scientists postulated that it might protect the heart against Adriamycin-induced cell destruction.

A group of mice was given a single injection of 15 mg/kg of Adriamycin. Malondialdehyde levels peaked after 4 days; 85 percent of the animals died from drug toxicity by the 30th day.

Another group of mice was pretreated with *alpha*-tocopherol, the principal constituent of vitamin E, 1 day prior to receiving an equal dose of Adriamycin.

No elevation of malondialdehyde was seen in this group of mice, and only 15 percent of the animals died from drug toxicity by the 30th day.

Examination of heart and other tissues from these animals confirmed that the vitamin E component blocked some destructive

(more)

VITAMIN E (CONT'D)

changes, Dr. McGuire says.

Free radical scavengers other than vitamin E did not protect mice from Adriamycin toxicity. Other agents tested included ethoxyquinone butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT).

When Adriamycin was given to mice on a weekly schedule of 5 mg/kg for 5 weeks, 100 percent of the mice died by 90 days. In a group of mice pretreated with vitamin E, 1 day prior to drug administration, only 60 percent of the mice died by 90 days.

Adriamycin is thought to achieve its anticancer effect by binding to DNA, the cell's hereditary material, and blocking DNA and RNA synthesis. This reaction may be different from that which causes deterioration of heart tissue, the NCI scientist points out.

Vitamin E pretreatment did not block the anticancer activity of Adriamycin in mice bearing th P388 transplanted leukemia. In fact, use of the vitamin led to increased survival by permitting higher doses of the anticancer drug to be administered.

Before these findings in mice can be applied to cancer patients receiving chemotherapy with Adriamycin, additional studies will have to be done, Dr. McGuire said. Information is needed on the effects of the vitamin on Adriamycin's toxicity to human heart tissue and activity against human cancer cells.

Also, the doses of the vitamin required for protection in the mouse would represent an equivalent dose for man higher than ever before used.

#

NIH WILL HOLD OBESITY CONFERENCE IN OCTOBER

A Conference on Obesity and the American Public: A Task Force Analysis and Recommendations for Public Action will be held October 20-22, 1977, at NIH in Bethesda, Maryland.

In spite of increasing attention in recent years, obesity remains one of our Nation's major health problems, with an estimated 30 to 50 million Americans affected. Most other affluent nations are similarly affected.

The three-day scientific meeting aims to analyze the background information in several areas associated with obesity, and to recommend needs for research and areas of action for a positive attack against this broad and prevalent problem.

The conference is sponsored by the Fogarty International Center (FIC) in conjunction with the Nutrition Foundation, the National Council on Obesity, the National Institute of Child Health and Human Development (NICHD), the National Institute on Aging (NIA), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD).

#

September 1977

DRR RESEARCH ANIMAL DIRECTORY AVAILABLE

A 56-page directory describing the animal resources of NIH's Division of Research Resources (DRR) has been published and is available free.

Titled *Animal Resources, A Research Resources Directory,* the booklet is intended as a guide to scientists seeking resource assistance and collaboration involving animals in biomedical research.

In addition to the complete listing of NIH's major Primate Research Centers, the directory identifies animal diagnostic laboratories, animal information projects, animal reference centers, and special colony and model study centers currently supported by DRR.

The Directory indicates the services provided, areas of research interest, principal investigators or directors, addresses, and telephone numbers. A contact person is identified for each resource.

A geographic index is included, listing resources by state, and within each state. A map shows the locations of the Primate Research Centers and animal diagnostic laboratories throughout the country.

A single copy of *Animal Resources, A Research Resources Directory* may be secured by writing to the Research Resources Information Center, 1776 East Jefferson Street, Rockville, MD 20852, or by request from the Office of Science and Health Reports, NIH, Division of Research Resources, Bethesda, MD 20014.

#

Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

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NEWS&FEATURES FROM NIH

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August 1977

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August 1977

EPILEPSY COMMISSION ANNOUNCES FINDINGS OF ITS 18-MONTH STUDY

The Commission for the Control of Epilepsy and Its Consequences announced the findings of its 18-month study on August 29, 1977. Among its discoveries are two poignant Catch-22's affecting the more than two million Americans with epilepsy.

--Under present government regulations persons with epilepsy can receive financial assistance to purchase medication. If the medication works and they become seizure-free, they can no longer receive assistance to continue purchasing the drug.

--Persons with epilepsy who tell potential employers of their disorder are frequently turned down. If they conceal it and have a seizure on the job, they can be fired for lying.

"While many programs are available to meet the needs of the person with epilepsy," said Dr. Richard L. Masland, Executive Director of the Commission, "they are badly underutilized and widely scattered. The real need is to mobilize the resources we have and bring them into one comprehensive system to attack the problem. We must assign responsibility to individuals at key levels in the government and within 'the establishment' and make the system work. The person with epilepsy falls between the cracks because there is not a single, comprehensive, national approach to the problem."

On the state level, the Commission found 41 states lacked any focal program concerned with epilepsy. On the Federal level the only organized unit with the specific concern of epilepsy is the Epilepsy Research Branch, a medical investigation unit

(more)

of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

The Commission presented a National Plan for Action made up of more than 400 specific recommendations which pinpoint the problems, the solutions, and the individuals or organizations, both public and private, which must accept responsibility. The report called for Congress to take quick action regarding the modest direct investment that is proposed to make existing service programs more effective. These are in the areas of medical services, research and prevention, education and employment, social adjustment and mental health, public, patient and professional knowledge and understanding, and achievement of equality and independence through legal rights.

The Commission also proposed the creation of a Comprehensive Epilepsy Service Network, a direct-service system which would become a catalytic force to fill the gaps and stimulate current service agencies to better, more cost-effective performance. The system would facilitate the extension and implementation of existing medical and social technology. "The network would see that those working in the field of epilepsy are working together and toward a common goal," Dr. Masland said. "The greatest single problem is to improve the understanding of the disorder by the person with epilepsy, his family, professionals and the public. Perhaps more than in any other impairment, the person with epilepsy epitomizes the dilemma of the handicapped in our complex medical, educational, and social support system."

(more)

EPILEPSY (CONT'D)

Within the Comprehensive Network a patient who has epilepsy would have access to a three-tier system which would bring medical technology and therapeutic skills to him more rapidly. He would know where to turn and to whom to turn for help which would be available to him quickly.

"Ignorance, superstition, and misconceptions about the disorder at every level of our society continue to plague the person with epilepsy and a massive information and education program is essential if this national plan is to work," said Dr. Masland.

The central Federal Office would have attached to it a National Information Center on Epilepsy. This center, acting in concert with voluntary organizations such as the Epilepsy Foundation of America, would conduct a large-scale public education program informing every national sector about the nature of epilepsy. This program would also stress the relatively simple preventive measures, such as seat belt use, proper screening, and pre-school vaccination programs, that would go far in reducing the incidence of epilepsy.

Through these information efforts, it is hoped a better climate can be created for the person with epilepsy in finding employment, acquiring insurance, and gaining social acceptance.

"The Action Plan represents a balanced approach to the problems of epilepsy," says Dr. Masland. "It provides a network of improved social and medical care for citizens with epilepsy, enabling them to make their fullest contribution to society. At

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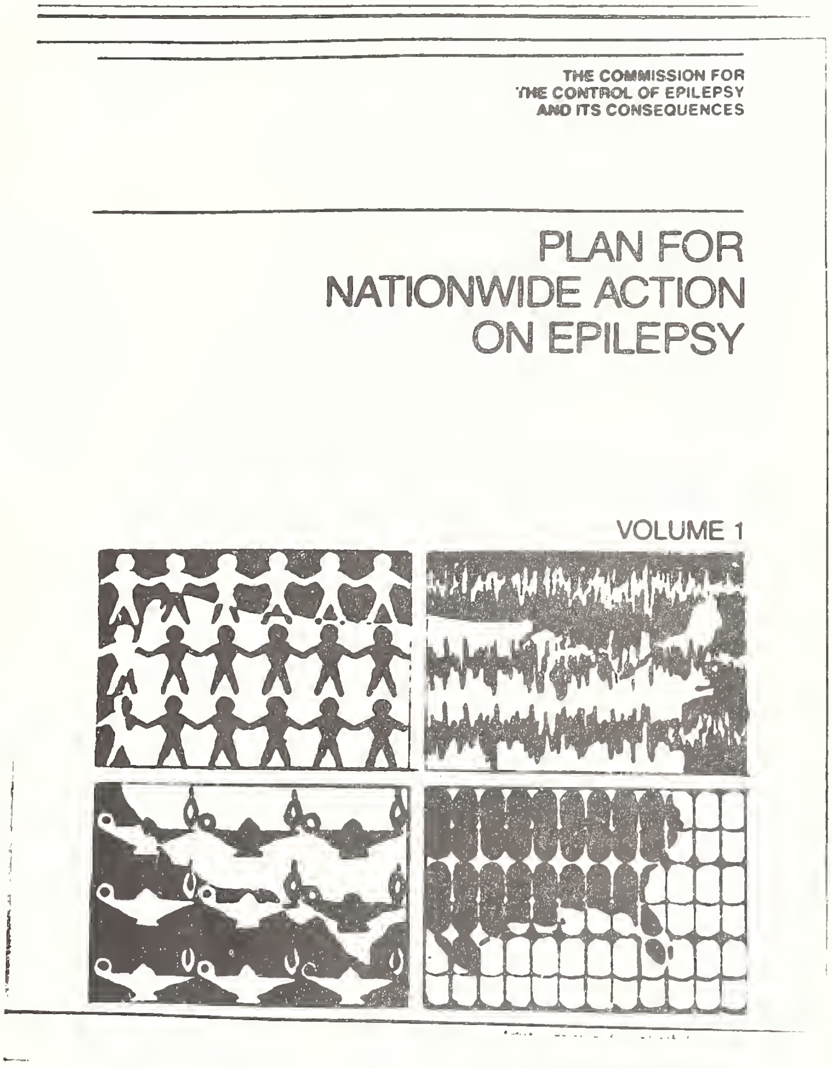
the same time it prepares society to accept that contribution. All too often it is not epilepsy itself, but society's reaction to it which creates the disability."



THE COMMISSION FOR
THE CONTROL OF EPILEPSY
AND ITS CONSEQUENCES

PLAN FOR
NATIONWIDE ACTION
ON EPILEPSY

VOLUME 1

Press copies of the Epilepsy Commission's "Plan for Nationwide Action on Epilepsy" will be available when they arrive from the printer this Fall. (N I H Photo #1601)

(more)

EPILEPSY (CONT'D)

Richard L. Masland, M.D., Executive Director of the Epilepsy Commission, described the findings of the Commission's 18-month study during a press conference on August 29. More than 60 media people from wire services, newspapers, magazines, television and radio stations, and professional publications covered the press conference. (N I H Photo #1602)

(more)

EPILEPSY (CONT'D)

The Epilepsy Commission studied the use of the drug, sodium valproate, in various countries. (N I H Photo #1603)

#

NEW CLUES FOUND IN STUDY OF CATARACT

An epidemiologic study of factors that may be associated with increased risk of eye disease and blindness has uncovered new clues for research to prevent cataract and macular degeneration--leading causes of blindness in the United States.

In the Framingham Eye Study, a four-year cooperative investigation by NIH's National Eye Institute and the Boston University School of Medicine, eye examination data were correlated with information on 550 health-related factors obtained from 2,675 residents of Framingham, Massachusetts. These individuals have been participating in an NIH study of heart disease risk factors since 1948.

According to the Study's principal investigators, Harold A. Kahn, former Chief of NEI's Office of Biometry and Epidemiology and now professor of epidemiology at Johns Hopkins University School of Hygiene and Public Health, and Howard M. Leibowitz, M.D., Chairman of the Department of Ophthalmology, Boston University School of Medicine, the most important findings are:

* Framingham residents with *senile cataract* were found more likely to have increased levels of a type of blood fat (serum phospholipid), high nonfasting blood sugar levels, and high blood pressure. Associations with aging-related factors were also found, as expected. Only diabetes has been previously reported as a risk factor for senile cataract. Prevalence of cataract for both sexes was almost five percent for ages 52-64, 18 percent

CATARACT (CONT'D)

for those aged 65-74, and 46 percent for the 75-85 age group.

* Persons with *senile macular degeneration* showed a positive association with increased blood pressure, enlarged left side of the heart (ventricular hypertrophy), a history of lung infection, and aging-related factors. Macular degeneration was also more common among women than men. Prevalence of macular degeneration for both sexes was two percent for those aged 52-64, 11 percent for those aged 65-74, and 28 percent for the 75-85 age group.

Mr. Kahn and Dr. Leibowitz hope that further study of their preliminary findings will ultimately provide clues to the causes of eye disease as the well-known Framingham Heart Study first identified major risk factors for coronary disease. They caution that the Eye Study's preliminary findings may be a mix of real and chance associations and therefore emphasize that these results must be replicated in an independent population before they can be considered as risk factors for eye disease.

Mr. Kahn, Dr. Leibowitz, and their associates published their findings in the August, 1977, issue of the *American Journal of Epidemiology*.

#

DEAF TODDLERS INVENT THEIR OWN SIGN LANGUAGE

Young deaf children who have never had any training in sign language have the capacity to invent their own sign-language "words." The children even devise their own syntactic rules for combining those words into complex phrases, according to a recent study partially supported by NIH's National Institute of Child Health and Human Development (NICHD).

Investigators Susan Goldin-Meadow of the University of Chicago and Heidi Feldman of the University of California at San Diego studied the communication skills of six deaf children ranging in age from 17 months to 4-1/2 years. In each case, the parents had decided not to expose the child to standard sign language in the hope of encouraging him or her to talk.

Nevertheless, videotaped observations of the children and their hearing mothers showed that the children were indeed using sign language.

Each child had developed a rich vocabulary of gestures to designate actions, objects,and characteristics of objects. One child, David, used 210 different sign-words of this sort.

Simple sign-words were often combined into two-sign or multi-sign phrases. For instance, David reacted to a picture of a shovel by pointing downstairs to the storage area where an actual shovel was kept, making a digging motion with his fists, and pointing downstairs again. In this one phrase he had commented on both the use of the shovel and its location.

(more)

DEAF (CONT'D)

Analysis of thousands of conversations in home-made sign language showed that deaf children may actually surpass their mothers in linguistic inventiveness.

The child exhibits as large a vocabulary of sign-words as the mother, but the specific gestures involved are not necessarily the same as those of the mother. Apparently the children are inventing rather than learning most of their sign-words.

Some children learn to use complex combinations of sign-words before their mothers do.

Most deaf children are fairly "grammatical" in their use of home-made sign language. That is, the child is likely to follow a consistent pattern when combining sign-words into phrases. Typically, the child will indicate the object to be acted upon (e.g., a jar) before indicating the action to be performed (e.g., twisting the lid off the jar).

Goldin-Meadow and Feldman conclude that "even under difficult circumstances, the human child reveals a natural inclination to develop a structured communication system." Given exposure to the basic idea of communication, children can and do generate their own language.

Goldin-Meadow and Feldman reported their findings in *Science*, Vol. 197, July 22, 1977.

#

DOCTORS' PERSONAL VIEWS ON ABORTION ARE COMPILED

A survey of Maryland obstetricians and gynecologists indicates that the pattern of providing abortion services is shaped in large measure by physicians' personal feelings toward patients and the abortion procedure itself.

Patient management and fee schedules are both largely determined by these attitudes, the study suggests.

The investigators found that physicians who reported a high degree of satisfaction with their patients generally were those with a largely middle-class, predominately white practice.

These doctors were less likely to require a minor to obtain parental consent; they tended to charge lower, but not the lowest fees, and were less likely to accept Medicaid or to ask for payment in advance.

The survey team found that the more disturbed a doctor claimed to be by the abortion procedure per se, the more likely he or she was to require consent from a patient's spouse or parent. Moreover, these physicians were also more apt to charge lower fees for performing abortions, and to accept Medicaid or private insurance as full payment for their services.

These findings lead the investigators to conclude that the lower professional fees and more liberal fee policies of the more disturbed physicians indicate that these physicians are reluctant to profit from a procedure that they find personally disagreeable.

Further support of this conclusion is the finding that physi-

(more)

cians who are the most liberal -- those who feel abortion should be readily available and that consent from spouse or parent is unnecessary -- charge relatively higher fees and are more likely to ask for payment in advance, according to the research team.

The survey was conducted by Constance A. Nathanson of the Johns Hopkins University School of Hygiene and Public Health and Marshall H. Becker of the Johns Hopkins University School of Medicine. The study was supported by the NIH's National Institute of Child Health and Human Development.

The Hopkins team surveyed 443 (94 percent) of the ob/gyn specialists with any private practice in the State. Of this total, 312 also completed a supplemental mail questionnaire. Data were collected during the winter of 1975-76.

Nearly 77 percent of the physicians responding reported that they favored the Supreme Court decision liberalizing abortion practices, a consensus that corresponds with previous national surveys of U.S. physicians. The strongest pocket of resistance to abortion among physicians comes from those whose religion officially forbids it, primarily Catholics. Only 15 percent of the Catholic physicians contacted perform any abortions at all.

Despite the apparent high levels of support for liberal abortion practices, some physicians experience considerable personal disturbance over the abortion procedure, according to the Hopkins team. In the Maryland survey, 42 percent of the physicians who perform abortions reported themselves to be "often" or "sometimes"

(more)

disturbed by their role in this procedure; of those who reported these feelings, 37 percent said that they are at least "moderately" disturbed.

Other findings to emerge from the study include:

* physicians surveyed reported performing a median 3.3 first trimester abortions and 1.2 second trimester abortions per month

* women obstetricians were less likely to perform abortions than men; 43 percent of the women would perform first trimester abortions and 19 percent would do second trimester procedures; the corresponding figures for male obstetricians are 63 percent and 35 percent

* 71 percent of the physicians surveyed felt Medicaid benefits should be available for abortions

* 57.9 percent do not accept Mediciad payment for abortion and 69 percent will not accept private insurance as complete payment if the insurance will not cover all of their usual fee

The study was reported in the July/August 1977 issue of *Family Planning Perspectives* by the two principal investigators.

Editor's note: This study was conducted and published prior to the newly implemented ban on Federal spending for most abortions. Since the announcement of that ban, the State of Maryland has said that it will continue to pay for the abortions of indigent women, at least for an interim period.

#

August 1977

VOLUNTARY STERILIZATION CONTINUES TO GAIN ON "PILL"

Results of recent analysis of a 1975 survey indicate that for the first time voluntary sterilization is approaching the popularity of the Pill as the birth control method of choice for U.S. couples.

That year, the estimated number of surgically sterilized couples (7.9 million) exceeded the number using the Pill (7.1 million). Even when these figures are adjusted to discount sterilization operations which were mandated by medical reasons and not purely for contraceptive purposes, the total (6.8 million) is very close to the number of Pill users.

Sterilization is the method of contraception most often chosen by couples who have been married more than 10 years or by those who have had all the children they want.

The Pill remains the most popular method of birth control only among women married less than 10 years.

These findings are from a 1975 National Fertility Study (NFS) conducted by the Office of Population Research at Princeton University. Data collected from the 1975 survey were compared with information gathered during similar NFS surveys conducted in 1965 and 1970. In addition, some tabulations from the 1973 DHEW National Survey of Family Growth were included.

The three NFS surveys were conducted under contract from the Center for Population Research of NIH's National Institute of Child Health and Human Development.

(more)

STERILIZATION (CONT'D)

The results of the surveys tend to confirm that the decade preceeding 1975 was marked by a dramatic swing toward use of those forms of contraception generally accepted in medical practice as being the most reliable. These methods include the birth control pill, sterilization, and intrauterine device (IUD).

At the beginning of the decade, only slightly more than one-third of married couples practicing contraception were using one of these methods; by 1975, an estimated three out of four couples were using one of them.

Of the 3,329 women interviewed in 1975, nearly a third (31.3 percent) reported that either they or their husband had been sterilized. Among women who intended to have no more children, this figure climbed to 43.5 percent, while percentages for those married for more than 10 years ranged from 43.3 percent to 55.7 percent, with the higher percentages recorded for those who had been married longest.

Thirty-four percent of the sample said that they were taking the birth control pill, but this percentage drops sharply with the duration of marriage. Only about 10 percent of women married 20 years or more use the Pill.

Nearly 65 percent of women married less than five years reported using the Pill, an increase of about eight percent since 1970. This group could be expected to include the largest proportion of women who intend to have more children.

These findings indicate that use of the Pill predominates among the young and the newly married whereas sterilization is

(more)

being increasingly employed by older couples who have completed their families.

Use of alternative methods of birth control -- the IUD, the diaphragm, the condom, withdrawal, foam, and rhythm -- has generally declined. There are some exceptions, however. A summary includes:

* IUD -- Use of the IUD among younger women has declined; only among women married more than 20 years has there been a slight increase in the use of the IUD.

* Diaphragm -- Its use is declining, especially among women who do not plan any more children. Only among women who expect to have additional children is there some indication of an increase in use, suggesting that use of the diaphragm may be increasing among young women who are using contraception to space their pregnancies. Less than five percent of women in virtually every category studied report using the diaphragm, however.

* Condom -- Use of the condom has dropped by half between 1965 and 1975. The only apparent exception to this is among couples who have been married less than 10 years. Use declined among couples in this bracket from 1965 to the period between 1970 and 1973 when a small upswing was noted.

The slight increases in use of the condom and diaphragm among young couples, according to the investigators, may be attributable to recent concern about the safety of the Pill and certain types of IUD's.

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STERILIZATION (CONT'D)

NFS surveys were limited to currently married white women who have been married only once, who have been married less than 25 years, and who married before the age of 25. The study design also required that the husbands have been married only once.

The study was reported in the July/August 1977 issue of *Family Planning Perspectives* by Charles F. Westoff, co-director of the study, and Elise F. Jones.

#

NEWS & FEATURES From NIH

August 1977

A PROTEIN IS FOUND TO INHIBIT IMMUNE RESPONSE

A protein present in early embryonic life and in certain types of cancer, α- fetoprotein (AFP), inhibits the immune response by inducing the formation of cells that regulate antibody production.

This finding, according to investigators in Sweden whose work is partially supported by NIH's National Institute of Allergy and Infectious Diseases, may help explain AFP's role in protecting the fetus from rejection by its mother, as well as its association with certain diseases.

Suppression or blocking of the normal immune response is believed to be involved in a mother's "immune acceptance" of the fetus, and in the development of certain diseases, such as cancer. How this blocking occurs is not well understood, but intermediary substances are thought to be involved.

Normally absent after fetal life, AFP has been found in the blood of liver cancer patients, and in patients with other diseases marked by poor immune responses. Although its function is unknown, AFP has been shown in prevous studies to be an immunosuppressive agent in animals and in humans. How AFP exerts this effect has not been understood, but evidence has indicated that it may indirectly inhibit the immune response by activating regulatory cells.

In the reported study, the scientists prepared cell cultures using normal mouse adult spleen cells, as a source of lymphocytes, to which they added either AFP obtained from mouse amniotic fluid (MAF), MAF itself or normal mouse serum. Some of the cells from

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PROTEIN (CONT'D)

each group were removed and cultured again with sheep red blood cells. The immune suppressive activity of the components of the cultures could then be determined by observing the immune response or the lack of it to the sheep red blood cells. This response is measured by the production of antibody-forming cells.

In all the cultures tested, the scientists found that antibody production was significantly suppressed when spleen cells were precultured with either MAF or MAF-derived AFP. Based on previous studies, the scientists reasoned that AFP was the factor in MAF responsible for this suppressive activity. In addition, maximum suppression was observed after several days indicating that AFP suppresses the immune response indirectly by inducing the formation of certain types of cells.

Antibodies are usually produced by a self-regulating system controlled by two major types of immune response cells; T cells or thymus-derived lymphocytes and B cells or thymus-independent lymphocytes. In most instances, B cells produce antibodies with the assistance of a subpopulation of T cells, known as helper T cells, while another T cell subpopulation (suppressor T cells) inhibits the response. Sometimes, B cells alone can produce antibodies.

Since antibody production involves a complex interaction of cells, their next step was to find out which immune response cells were being induced by AFP. The researchers cultured normal mouse spleen cells, purified splenic T cells and spleen cells from thymus-deficient mice in either MAF or normal mouse serum and tested for antibody suppression. They found suppressor activity in the

(more)

MAF-precultures with purified T cells and in those with normal spleen cells. No antibody suppression, however, was demonstrated in pre-cultures of spleen cells from thymus-deficient (T cell deficient) mice.

Thus, the investigators concluded that T lymphocytes were responsible for suppressing the antibody response observed with AFP. In addition, the researchers found that the suppressor T cells induced by AFP inhibited only T cell-dependent antibodies, probably by suppressing helper T cells. Antibodies produced by B cells alone (T-cell independent) were unaffected.

Based on these findings the researchers suggest that AFP protects the fetus by inducing the formation of suppressor T cells. They state that these results are in agreement with previous studies in newborn mice where high concentrations of AFP coincided with a significant number of suppressor T cells. In humans, T lymphocytes from newborns have been shown to function as suppressor cells inhibiting the ability of the mother's lymphocytes to divide and multiply.

The next step, planned by the investigators, is to find out how AFP induces suppressor T cell formation.

The report of this research by R. A. Murgita, E.A. Goidl, S. Kontiainen and H. Wigzell from the Department of Immunology, Uppsala University, Uppsala, Sweden, appeared in the May 19, 1977 issue of *Nature*.

#

BACTERIAL "MATING" MAY SPREAD PENICILLIN RESISTANCE

The sex life of gonococci, the bacteria causing human venereal disease, may itself provide clues as to how and why penicillin-resistant strains of the organism have recently appeared in various parts of the world. This finding, by scientists at the University of Washington, Seattle, has serious implications not only for the control of gonorrhea but also for other diseases, such as meningitis, caused by related but currently penicillin-sensitive organisms. This work is funded by NIH's National Institute of Allergy and Infectious Diseases.

In bacteria, transfer of hereditary information may take place in a variety of ways. For example, *transformation* involves the absorption by a bacterial cell of DNA (deoxyribonucleic acid) chemically extracted from a donor cell. In contrast, *conjugation* consists of the transfer of genetic material as a consequence of cellular contact between sexually differentiated bacteria. The sex of a bacterial strain depends upon the presence (male) or absence (female) of a genetic structure known as the sex factor. Of all phenomena of genetic transfer in bacteria, conjugation is the one which most closely resembles the sexual pattern of higher forms of life.

Earlier work by the Seattle investigators showed that the ability of gonococci to make a penicillin-destroying enzyme (β-lactamase) and thus to become completely resistant to the ordinarily curative drug was transferred from one strain to another by circular

(more)

bits of DNA known as plasmids. In studying β-lactamase-producing gonococci from the Far East, Drs. Marilyn Roberts and Stanley Falkow noted that the bacteria differed in so many ways that it seemed unlikely that they all arose from a single ancestral resistant strain.

For this reason, the scientists investigated the possibility that the gonococcal R (for resistance) plasmid DNA could have been disseminated by transformation, historically the only known mode of genetic transfer among gonococci and related species. Drs. Roberts and Falkow found, however, that the gonococci were refractory to transformation by closed circular plasmid DNA and, therefore, that dissemination of the gonococcal R plasmids was not likely to be through transformation.

In a second set of mating experiments to examine the conjugative properties of gonocci, β-lactamase-producing strains were used as the donors (males) and the recipient (female) strain was a non-β-lactamase producer. The investigators found that successful transfer of the R plasmid was observed only when the donor gonococci contained a second large indigenous plasmid. This plasmid was assumed to have "sex factor" activity and through conjugation to promote the transfer of the smaller coexisting R plasmid. Furthermore, it was found that in overnight mating experiments, considerable numbers of gonococcal recipients received the large "sex factor" plasmid along with the R plasmid and thus became capable of passing along the latter.

In view of the ease with which R plasmids can seemingly be

(more)

transmitted among various strains of gonococci, the investigators express concern that, through the process of conjugation other related bacterial species, now presently penicillin-sensitive, may also become β-lactamase producers, and therefore resistant to penicillin or penicillin-based antibiotics.

A report on this work, and an accompanying editorial, appeared in the April 14, 1977, issue of *Nature*.

#

V-Y (WARDILL) REPAIR IMPROVES SPEECH RESULTS

Children with cleft palates develop less nasal, more natural speech when the defects are repaired with V-Y (Wardill) rather than the Von Langenbeck surgical procedure, according to preliminary studies supported by NIH's National Institute of Dental Research.

The University of Iowa investigators have found that neither operation interferes appreciably with growth during the time span for which they have records.

From 1961 to 1968 the Iowa surgeons used the Von Langenbeck method of closing the palate. They note that about half of the surgeons in the United States and Canada have considered this method satisfactory. However, the V-Y or Wardill procedure designed to lengthen as well as close the palate, has been widely used in Europe and is now fairly common in this country. Surgeons have debated which type of repair gives more normal growth, appearance, and quality of speech.

Samir E. Bishara, D.D.S., Hans Enemark, D.D.S., and Rosemary F. Tharp, M.A., compared the effects of these two operations on craniofacial growth and appearance. They measured skulls radiographically, and took full face and profile photographs. The growth studies were done both on Danish and American, white, female children and adolescents all of whom had required only palatal repairs. The children with cleft palates were compared with matched normal individuals in each country.

(more)

SPEECH (CONT'D)

The investigators found that the two procedures have similar effects upon facial growth in both vertical and front-to-back dimensions. In general, younger children with clefts had more retruded, shorter jaws than normal children. By age 17, the relationships between various parts of the face were similar in normal and corrected individuals although in X-ray photographs the upper jawbones of corrected patients were usually somewhat shorter in relation to the lower.

To evaluate speech results, Charles J. Krause, M.D., Rosemary F. Tharp, M.A., and Hughlett Morris, Ph.D., compared speech in groups of American patients treated by each method. Of the 118 patients who had the V-Y surgery for all types of palatal clefts, 74 percent were judged to have competent speech. The mean age of this group was five years with a range of 2-10 years. Only 56 percent of 149 patients treated by the Von Langenbeck method had competent speech at a mean age of about 12 years with a range of 4-25 years.

The investigators found that following both types of operation poorer speech paralleled the severity of the cleft. Only when the clefts were limited to the soft palate and therefore less severe, did the Von Langenbeck operation result in better speech than the V-Y procedure, and even then the difference was not statistically significant.

Children's speech generally improves with age, therefore

(more)

SPEECH (CONT'D)

the scientists consider their findings preliminary because the V-Y treatment method has not been used in this country long enough to compare speech results from both procedures through adolescence.

According to the Iowa group, unless further study shows clear differences on other grounds, the better speech resulting from the V-Y technique should be a prime reason for using that method to repair palatal clefts.

These findings have been reported in the *Cleft Palate Journal* and in the *Angle Orthodontist*.

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NEWS & FEATURES From NIH August 1977

NIH STUDIES CAUSES OF PERINATAL DEATH

In a nationwide study of 53,518 pregnancies, the underlying causes of 80 percent of infant perinatal deaths were identified; 17 percent of the deaths were due to amniotic fluid infections and 11 percent to the detachment of the placenta prior to birth.

Between 1959 and 1966, more than 200 pathologists from 12 university-affiliated hospitals in different regions of the U.S. performed 1,435 autopsies of the 1,993 perinatal deaths occurring between 20 weeks of gestation and 28 days after birth. They also conducted 36,259 placental examinations evaluating the clinical, placental, and postmortem material from all perinatal deaths using standardized diagnostic procedures.

Dr. Richard L. Naeye of Pennsylvania State University College of Medicine, Hershey, assembled and cataloged the perinatal death statistics in the Collaborative Report Project, which was organized by the National Institute of Neurological and Communicative Disorders and Stroke.

The ethnic composition of the group was 46 percent white, 46 percent black, seven percent Puerto Rican, and the rest Orientals and other ethnic minority groups. No correlation was made between the socio-economic diversity of the ethnic groups with perinatal deaths.

Research indicated the leading cause of death, acute amniotic fluid infection, as causing pneumonia in the unborn and newborn. The second leading cause, abruptio placentae, included not only

(more)

placental detachment but also external bleeding. Additionally, in post mortem examination of the fetus, hypoxia (low oxygen content in expired air) was noted. Other findings in the diagnosis of several cases disclosed:

* Compression deaths included breech deliveries in which the head compressed the cord, cases of cord prolapse, and instances where the cord was tightly wound around the infant's neck.

* The placenta was 40 percent or more below normal weight for gestational age and there was no other explanation for death.

* Large tumors containing effused blood (hemotomas) were found during autopsy of 91 percent of cases that involved birth traumas.

* Neonates showed gross microscopic characteristics of undernutrition without any known cause except maternal weight loss or low weight gain during pregnancies.

* Perinatal death was ascribed to congenital anomalies when they were severe and incompatible with fetal or neonatal survival.

* In congenital syphilis, all cases were confirmed by the finding of spirochetes in the infants' tissues.

A 1964 comparative study of perinatal deaths ranked the infant mortality rate of the U.S. higher than Denmark, England, the Netherlands, Norway, Scotland, and Sweden. U.S. infant deaths were 75 percent higher than the lowest rate of Sweden.

Further, statistics showed that 96 percent of U.S. births

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were in hospitals with attending physicians whereas in several western European countries, trained nurse-midwives conducted normal deliveries which had no major complications.

In this study, 73 percent of perinatal deaths were due to disorders in which the pathogenesis was so incomprehensible that it was not clear how they can be prevented.

The report noted that in recent years, the frequency of U.S. perinatal deaths has been slowly decreasing without specific programs having been adopted to control any of these disorders.

It is hoped that the trend of decreasing deaths will continue as more research is conducted to gain more knowledge about the prevention of these disorders. This research was reported in the July 18, 1977 issue of the *Journal of the American Medical Association.*

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August 197

FIC ANNOUNCES RESEARCH FELLOWSHIPS TO SWEDEN AND SWITZERLAND

The Fogarty International Center, National Institutes of Health, has been asked to announce that the Swedish Medical Research Council and the Swiss National Science Foundation will each make available in 1978 several research fellowships to qualified U.S. biomedical scientists. Fellowships are awarded usually for a 12-month period to scientists in a formative stage of research careers, preferably with less than 10 years of postdoctoral experience, for training in basic or clinical areas of biomedical research.

Applications must include a complete and explicit plan for the research training and evidence of acceptance by a training institution and preceptor. Stipends levels depend upon age and experience but range from approximately $10,000 to $14,000. Other benefits include travel costs and allowances for dependents.

Applications are processed and initially reviewed by the Fogarty International Center. The deadline for both Swedish and Swiss applications is January 1, 1978. Further information and application materials for either program may be obtained from The Scholars and Fellowships Program Branch, Fogarty International Center, National Institutes of Health, Bethesda, MD 20014.

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NEWS & FEATURES From NIH

August 1977

BREAST CANCER SCREENING IS TOPIC OF NIH MEETING

The issue of breast cancer screening will be examined at a meeting at the National Institutes of Health (NIH), on September 14-16, 1977.

Sponsored by the NIH and the National Cancer Institute (NCI), the meeting will deal with large-scale breast cancer screening, including the use of X-ray mammography in routine screening programs.

A panel of leading scientists and clinicians, along with lay people, will hear a series of presentations by individuals who have been active in the continuing discussion of breast cancer screening. Brief presentations will also be made by other concerned professionals and the public.

Following the formal presentations, the panel will attempt to reach a consensus on modalities for breast cancer screening in terms of risk and benefit.

Chairman of the NIH/NCI consensus development meeting is Samuel O. Thier, M.D., Department of Internal Medicine, Yale University.

The panel will consider the question of screening to detect breast cancer in apparently health women. The screening techniques to be considered are medical history, physical examination, mammography, thermography and breast self-examination. They also will consider alternatives to screening programs and populations and ages appropriate for screening.

(more)

BREAST CANCER (CONT'D)

The panel is expected to make recommendations for breast cancer screening programs now available through medical care systems. If indicated, the panel will define clinical trials required to provide additional information pertinent to breast cancer screening.

Among the materials to be presented to the panel are a review of three reports submitted to the NCI in March 1977. These evaluated the potential benefits of mammography based on data from the 1960s Health Insurance Plan (HIP) Study of Greater New York and the possible risks for breast cancer from exposure to ionizing radiation. The panel also will consider a new report to be received from a working group studying data from the Breast Cancer Detection Demonstration Project. This screening project is cosponsored by the NCI and the American Cancer Society.

The sessions will take place from 8:30 a.m. to 6 p.m. daily in the Masur Auditorium of the NIH Clinical Center. All sessions are open to the public.

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